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**The Chemistry of
Technetium in Medicine**

*by Joseph Stengman
and Wilfrid C. Eckelman*

Nuclear



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Nuclear Medicine

THE CHEMISTRY OF TECHNETIUM IN MEDICINE

by

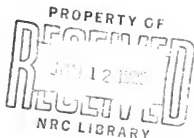
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The Committee on Nuclear and Radiochemistry is one of a number of committees working under the Board on Chemical Sciences and Technology of the Commission on Physical Sciences, Mathematics, and Applications of the National Research Council. Its members are drawn from academic, industrial, and government laboratories and represent the areas of nuclear chemistry, radiochemistry, and nuclear medicine.

The committee has concerned itself with those areas of nuclear science that involve the chemist, such as the collection and distribution of radiochemical procedures, specialized techniques and instrumentation, the place of nuclear and radiochemistry in college and university programs, the training of nuclear and radiochemists, radiochemistry in environmental science, and radionuclides in nuclear medicine. A major interest of the committee is the publication of the Nuclear Science Series of monographs on Radiochemistry, Radiochemical Techniques, and Nuclear Medicine.

The committee has endeavored to present monographs that will be of maximum use to the working scientist. Each monograph presents pertinent information required for radiochemical work with an individual element or with a specialized technique or with the use of radionuclides in nuclear medicine.

Experts on the various subjects have been recruited to write the monographs. The U.S. Department of Energy sponsors the printing of the series.

The present monograph is a review of the current status and use of technetium in medicine. This monograph, one of the series on Nuclear Medicine, is published as part of our continuing effort to update, revise, and expand the previously published monographs to keep them current and relevant.

Richard L. Hahn, *Chairman*
Committee on Nuclear and Radiochemistry

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I.

Introduction

Technetium, element #43 in the Periodic Table, was discovered in 1937 by Perrier and Segrè, who separated it from a molybdenum deflector plate after some years of deuteron irradiation in the Berkeley cyclotron.⁽¹⁾ At present there are 17 known isotopes, all radioactive, and 6 nuclear isomers. Of these, the short-lived nuclear isomer ^{99m}Tc ($T_{1/2} = 6.03 \text{ h}$) is used in nuclear medicine, and the much longer-lived ^{99}Tc ($T_{1/2} = 2.1 \times 10^5 \text{ years}$), which is available from uranium fission, is used to establish the general chemistry of the element at conventional chemical concentrations.⁽²⁾ Three shorter-lived isotopes, ^{92}Tc ($T_{1/2} = 4.44 \text{ minutes}$), ^{93}Tc ($T_{1/2} = 165 \text{ minutes}$) and ^{94m}Tc ($T_{1/2} = 52 \text{ minutes}$) which are positron emitters, may find use in positron emission tomography.⁽²⁾

The first injection of $\text{Na } ^{99m}\text{TcO}_4$ into a human was made in 1961,⁽³⁾ following the development of the so-called Brookhaven generator.^(4,5) Its use in diagnostic medicine expanded rapidly. A bibliography of medical applications showed some 1600 references in the period 1965-1971. In 1970 it was estimated that more than 2000 daily diagnostic procedures based on ^{99m}Tc were carried out in the United States alone.^(6a) In 1985, the market for ^{99m}Tc generators was \$30 million and the market for instant kits to be used with the generator was an additional \$30 million. At the present time more than three quarters of the routine nuclear medicine diagnostic procedures use ^{99m}Tc .^(6b) Its radiation characteristics are excellent for this purpose. Its half life is 6.03 hours, it emits gamma ray photons, but no beta particles and only low energy or low frequency Auger electrons. The predominant photon energy - 0.1405 MeV - is almost totally absorbed in the thin thallium-doped sodium iodide single-crystal slabs used in the various cameras.⁽⁷⁾ Although other generator systems offer some real advantages over the ^{99}Mo - ^{99m}Tc generator,⁽⁸⁾ its use is increasing.

The chemistry of ^{99m}Tc in medicine is another matter. There is no single unifying theme in this topic, except for the successful end-use of various preparations for clinical diagnoses. Complexities in the chemistry, especially in aqueous solution, make it difficult to assign an overall role to its behavior in medically useful radiopharmaceuticals as one might do in the case of much better understood elements like nickel and cobalt. At the same time very little is known about the metabolism and the ultimate fate of the various ^{99m}Tc -containing radiopharmaceuticals which have been injected. Because of the lack of a single theme the procedure which will be followed in this review will be to describe the relevant chemistry of technetium in its various oxidation states. In the case of the pertechnetate anion, TcO_4^- , no distinction will be drawn between the chemistry of ^{99}Tc (millimolar) and that of $^{99m}\text{TcO}_4^-$ (nanomolar range). For the reduced states of technetium, we shall present the chemistry of appropriate complexes for the more concentrated solutions by oxidation state and then discuss the chemistry of radiopharmaceutical preparations.

Technetium is a second-row transition metal. It is in group VIIa of the Periodic Table,⁹ below manganese and above rhenium. Its neighbors are molybdenum, #42, and ruthenium #44. The second and third-row transition metals show much greater complexities in their chemical behavior than the first-row elements. Their spin-orbital coupling constants are much larger, as are ligand field splittings, leading to more electron pairing, with resulting low magnetic moments (except for d-3

states). The highest oxidation states are more stable than those of their first-row congeners, and the chemistry of the lower oxidation states becomes quite complicated, often exhibiting metal-metal bonding. Technetium itself can assume any oxidation state from +7 to 0. It resembles manganese to a limited extent, and rhenium to a much greater extent. In its compounds it exhibits coordination numbers from 4 to 9, and their crystal structures show great variety.⁽¹⁰⁾ In water, and of necessity our major interest is in its aqueous chemistry, many of its compounds hydrolyze, polymerize, and become colloidal. In this treatment, we shall draw upon the chemistry of rhenium compounds, which often resemble their technetium analogs, and occasionally on the chemistry of isoelectronic molybdenum compounds.

II.

Methods of Analysis of Technetium-99

Methods of analysis for total technetium are of limited direct interest in nuclear medicine, since the central analytical problem in that area is the determination of the quantity of technetium-99m in a particular chemical form rather than a determination of the total technetium present in a sample. Usually physical methods (with perhaps some preliminary chemical operations) suffice for the determination of total technetium. These methods include liquid scintillation counting,¹¹ neutron activation analysis,¹² atomic absorption,¹³ x-ray fluorescence¹⁴ and mass spectrometry.¹⁵

The pertechnetate ion in water shows strong absorption in the UV at 244 nm and 287 nm ($\epsilon = 5690$ and $2170 \text{ M}^{-1} \text{ cm}^{-1}$ respectively).¹⁶ In addition, a strong infrared band at 901 cm^{-1} , characteristic of the $\text{Tc}=\text{O}$ stretch, has been used.¹⁷

There are a number of spectrophotometric methods for the determination of technetium which have been developed over the years. In most of these, strongly colored complexes or chelates of technetium are formed, with high molar extinction coefficients. The chemistry is known in only a few of these. They are included here because two of them illustrate different relevant problems in technetium chemistry.

The first is the thiocyanate method of determination originated by Crouthamel.¹⁸ Concentrated ammonium thiocyanate (NH_4SCN) both reduces pertechnetate and forms complexes with the reduced forms in 3.5-4.0M sulfuric acid. A red-purple solution is produced. Acetone (60%V/V) markedly increases the absorbance at 510nm and 400nm. The molar absorptivity at 510nm is $47,500 \pm 500 \text{ M}^{-1} \text{ cm}^{-1}$. This product is soluble in organic solvents. A yellow complex in a lower oxidation state is also formed which absorbs at 400nm. This method is the basis of a projected official ASTM (American Society for Testing Materials) standard method for technetium analysis.¹⁹ Crouthamel, on the basis of the corresponding rhenium chemistry,²⁰ assigned the red complex to Tc(V) , and the yellow complex to Tc(IV) , and reported that while the red complex resisted oxidation, the yellow complex was easily reduced. Schwachau, Astheimer and Schenk also attributed the red complex to Tc(V) as the $\text{Tc}(\text{NCS})_6^{1-}$ anion, and the yellow complex to Tc(IV) as the $\text{Tc}(\text{NCS})_6^{2-}$ anion, and measured the standard redox potential in 1M H_2SO_4 which turned out to be +0.53 volts at 25.²¹ However, Trop et al who found that the hexahalometalate complexes of Tc(IV) were very difficult to oxidize to hexahalometalate complexes of Tc(V) ²² later reported the synthesis and purification of a purple compound, $(\text{Ph}_4\text{As})_2\text{Tc}(\text{NCS})_6$, verified by IR, Raman, conductivity and magnetic susceptibility measurements.²³ In acetonitrile it showed an absorption peak at 500nm with a molar absorptivity of 76,100. They also reported the synthesis and properties of yellow air-sensitive $(\text{Ph}_4\text{As})_2\text{Tc}(\text{NCS})_5$ with $\epsilon = 8,300$ at 410nm. The structure of Crouthamel's yellow Tc(IV) compound was elucidated. Polarographic measurements in acetonitrile showed a reversible one-electron transfer between Tc(III) and the Tc(IV) complexes; $E_{1/2}$ versus standard calomel was +0.18 volts. A more recent paper

*Molar Absorptivity from Anal. Chem 54:157 (1982)

by the same group was devoted to the synthesis and properties of a Tc(V) complex: $(\text{Ph}_4\text{As})_2\text{TcO}(\text{NCS})_5$.¹²⁴ In the presence of excess thiocyanate (in acetonitrile) this compound is easily reduced to mixtures of both the Tc(IV) compound, $\text{Tc}(\text{NCS})_6^{3-}$ and the Tc(III) compound $\text{Tc}(\text{NCS})_6^{2-}$. In short, the standard analysis for technetium in strongly acidic thiocyanate solutions probably involves the early formation of the Tc(V) complex, which is rapidly reduced by excess thiocyanate to a mixture of the Tc(III) and Tc(IV) complexes, absorbing at 400 and 510 nm respectively. This is in contrast to rhenium in which $\text{ReO}(\text{NCS})_5^{2-}$ (Re(V)) and $\text{Re}(\text{NCS})_6^{1-}$ (Re(IV)) are involved. This illustrates the complexity of technetium chemistry, as well as the danger of too readily accepting rhenium behavior as an exact model for technetium in all cases.

	<u>Crouthamel¹²⁴</u>		<u>Trop²²</u>	
	<u>Tc(V)</u>	<u>Tc(IV)</u>	<u>Tc(IV)</u>	<u>Tc(III)</u>
λ_{max}	510 nm	400 nm	500 nm	410 nm
ϵ	$47,500 \pm 500$	--	76,100	8,300
Color	red purple	yellow	purple	yellow

The second example is concerned with the use of thioglycolic acid, HSCH_2COOH , as an analytical reagent for technetium. The sulfhydryl group is the reductant in a test developed by Miller and Thomason.¹²⁵ They found that at pH 8 a green complex (λ_{max} 655 nm, $\epsilon = 1800$) was formed, but that in acid solution there was only general absorption in the range 350-500nm. Davison et al, attempting to synthesize a technetium complex of thioglycolic acid found a product which was derived from an impurity in a commercial preparation. This impurity was mercaptothioacetic acid, HSCH_2COSH , which made up 15% of the starting material, and which reacted preferentially relative to the thioglycolic acid itself, forming $\text{TcO}(\text{SCH}_2\text{COS})_2$.¹²⁶ In acetonitrile this compound showed two bands: at 415nm ($\epsilon = 3665$) and at 325nm ($\epsilon = 3100$). While large solvent shifts are possible, it is difficult to understand how the Miller-Thomason method avoided the formation of the mercaptothioacetate complex. Presumably the commercial material used by them was of high purity.

Electroanalytical methods of analysis (principally current-voltage curves) have also been used in the determination of ^{99}Tc . Since this is a complicated question, reference at this point is limited to analytical methods for total technetium, usually based on the electro-reduction of pertechnetate. In a phosphate buffer at pH 7 or KCl solution adjusted to pH 10, a linear relationship was reported between the pertechnetate concentration and the diffusion current.²⁷¹ Anodic stripping in 1M NaOH after deposition on a mercury drop has also been used.²⁶¹ A coulometric method at fixed potential in a tripolyphosphate solution in an acetate buffer at pH 4.7 was reported to give accurate and reproducible results.²²⁹ An amperometric method based on the electrogeneration of Sn(II) from Sn(IV) in a concentrated NaBr solution with HBr and the reduction of TcO_4^- by the generated Sn(II) reagent is said to be satisfactory.¹³⁰

III. Sources of Technetium-99m

Pertechnetate-99m is obtained in three ways: from a generator, as "instant technetium" by extraction, or as Tc_2O_7 by high temperature evaporation. In all three cases it is produced by the decay of molybdenum-99. The latter is either a fission product or is made by neutron bombardment of highly purified molybdenum metal in a reactor.

^{99}Mo decays mostly to the $^{99\text{m}}\text{Tc}$ metastable nuclide, and to a lesser extent (13%) directly to the long-lived ^{99}Tc nuclide.^{3(a,b)} There is therefore a modification of the equation which describes the growth and decay of $^{99\text{m}}\text{Tc}$ from ^{99}Mo . For a simple parent-daughter pair, in which the half-life of the parent is longer than that of the daughter, the pair will eventually enter a state of transient equilibrium. The number of daughter nuclei, (N_2) is related to N_1 , the number of parent nuclei at the same time, t , in the following equation:

$$\frac{N_2}{N_1} = \frac{\lambda_1}{\lambda_2 - \lambda_1}$$

where λ_1 and λ_2 are the decay constants for the parent and daughter respectively. This is the result of simplifying assumptions made on the general equation:

$$N_2 = \frac{\lambda_1}{\lambda_2 - \lambda_1} N_1^O \left(e^{-\lambda_1 t} - e^{-\lambda_2 t} \right) + N_2^O e^{-\lambda_2 t}$$

where N_1^O and N_2^O respectively are the number of parent and daughter atoms present at $t=0$. One may take N_2^O , the number of daughter atoms initially present, as zero. The condition for transient equilibrium is that $e^{-\lambda_2 t}$ is negligible compared to $e^{-\lambda_1 t}$. The accuracy of this assumption is a matter of personal decision but the second term represents a 1.2% contribution at 42 h. For the molybdenum-technetium system, the equation becomes:

$$N_2 = 0.87 \quad \frac{\lambda_1}{\lambda_2 - \lambda_1} N_1^O \left(e^{-\lambda_1 t} - e^{-\lambda_2 t} \right)$$

Expressed in terms of disintegration rates or activities, it becomes:

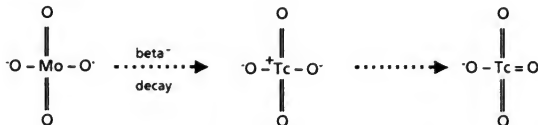
$$A_2 = 0.87 \quad A_1^O \frac{\lambda_2}{\lambda_2 - \lambda_1} \left(e^{-\lambda_1 t} - e^{-\lambda_2 t} \right)$$

If ^{99}Mo decayed only to $^{99\text{m}}\text{Tc}$, the ratio of activities of daughter to parent at transient equilibrium would be 1.10. However, because 13% of the ^{99}Mo nuclides decay directly to the ^{99}Tc ground state, the equation take the form:

$$\frac{A_2}{A_1} = 0.87 \frac{\lambda_2}{\lambda_2 - \lambda_1}$$

At transient equilibrium, the $^{99\text{m}}\text{Tc}$ radioactivity is 96.25% of that of ^{99}Mo . Long-lived ^{99}Tc atoms will be present in the generators from the decay of ^{99}Mo as well as from the decay of $^{99\text{m}}\text{Tc}$. The chemical consequences of the appearance of ^{99}Tc in the generator from both these decay processes (but mainly from the decay of $^{99\text{m}}\text{Tc}$) are discussed in the section on reduced $^{99\text{m}}\text{Tc}$ compounds.

The technetium which is produced in solution or on a column by the decay of molybdenum-99(VI) is largely in the oxidation state VII corresponding to the following equation, with no breaking of chemical bonds.



The retention of ligands by the technetium has been found to be true with various metal-organic and carbonyl complexes of molybdenum,^(32,33,34) as well as with molybdate itself.⁽³⁵⁾ It must also be the case for the direct decay of molybdenum to technetium-99, since the only difference in the decay schemes will be a small difference in the maximum energy of the molybdenum beta particle.

A. The Brookhaven Generator

The Brookhaven generator^(36a,b) consists of a column of about 5 grams of activated alumina, which has been acidified and treated with a sodium molybdate solution containing molybdenum-99. If the latter is a fission product, the specific activity will be very high, ($> 10^4 \text{ Ci/g}$), with very little carrier molybdate. If the molybdenum-99 is a reactor product, there will be many milligrams of carrier molybdate on the column.

In weakly acid solution the molybdate anion polymerizes, forming the $\text{Mo}_7\text{O}_{24}^{6-}$ homopolymer.⁽³⁷⁾ If aluminum ions are present, a stable heteropolymer, $\text{Al}(\text{Mo}_6\text{O}_{24})^{3-}$, is formed.^(38,39,40) While the structure of the molybdate polymer on activated alumina is not necessarily the same as that formed in aqueous acid, it can be concluded that aluminum ions on the activated alumina surface will bind some octahedral polymeric variety of MoO_3 groups, probably by the displacement of hydroxy groups coordinated to aluminum ions.⁽⁴¹⁾

The nature, properties and preparation of activated alumina have been described elsewhere in some detail.⁽⁴²⁾ It may have any composition from $\text{Al}_2\text{O}_3 \cdot \text{H}_2\text{O}$ (AlOOH) to $\text{Al}_2\text{O}_3 \cdot 0.1 \text{ H}_2\text{O}$. The materials used as catalyst beds are usually of high purity and are well-characterized with respect to structure (by X-ray diffraction, composition, surface area, and porosity). However, those used in

chromatography (and this includes most of the technetium generators in the past) are described in much more qualitative terms by a rather arbitrary test based on dye absorption which is called the Brockmann degree.⁽⁴³⁾

The pertechnetate anion in acid solution is adsorbed by sites on the alumina, and will be displaced by an added electrolyte. For convenience this is usually a solution of sodium chloride. In this respect, pertechnetate behaves like most univalent anions, which are readily displaced by salts of other univalent anions - salts like KCl or KNO₃. Polyvalent anions are very strongly held by acidified alumina, and are not significantly displaced by increasing concentrations of KCl or KNO₃. They can be displaced by other polyvalent anions. The extent of displacement increases with increasing eluant concentration.⁽⁴⁴⁾

Problems of chemical and radiochemical purity arise in the use of generators. Aluminum salt displacement from the column must be limited to less than 20 µg/ml of eluate for reactor material, and to half of that for fission-derived molybdate.⁽⁴⁵⁾ Aluminum must be analyzed colorimetrically, by reaction with Alizarin S or with aurin tricarboxylic acid. The USP method uses eriochrome cyanine.⁽⁴⁵⁾ Molybdenum-99 breakthrough is limited to less than 0.15 µCi per mCi of ^{99m}Tc at the time of use. Other gamma-emitting radioactive products in fission-based generators are limited to less than 0.5 µCi per mCi of ^{99m}Tc at the time of injection. ⁸⁹Sr, a beta-emitter, is limited to 6×10^{-4} µCi per mCi of ^{99m}Tc whereas ⁹⁰Sr is limited to 6×10^{-5} µCi Sr per mCi of ^{99m}Tc at the time of dosage. ¹⁰³Ru and ¹³¹I are also common contaminants, limited to 0.05 µCi/mCi of ^{99m}Tc.⁽⁴⁶⁾

There is a problem which arises in generators: a yield of pertechnetate which may be much less than expected. A large, and sometimes preponderant fraction of the expected pertechnetate remains on the column after elution. Two groups of investigators have concluded that the effect is due mainly to the chemical reduction of pertechnetate caused by the radiolysis of water by the molybdenum-99 beta particles. The reduction, however, is seen only in the presence of alumina.^(47, 48) The radiolysis of water produces solvated electrons, H atoms, OH radicals, HO₂ (from dissolved oxygen), H₂O₂ and H₂.⁽⁴⁹⁾ An encounter between a pertechnetate ion and a solvated electron will produce technetate, TcO₄²⁻ (confirmed in pulsed electron radiolysis studies).^(50, 51) In the absence of alumina, reduced technetium species are not observed in irradiated pertechnetate solutions.^(47, 48) However, in the presence of alumina, if the TcO₄²⁻ ion is formed on or near the alumina surface, it will be strongly adsorbed at an anionic site like any other polyvalent anion, and it will probably not encounter another technetate anion because of its high dilution, so that a disproportionation reaction between distant neighbors is unlikely. Oxygen reduces the adsorption of technetium by the columns, probably by scavenging solvated electrons, and forming O₂⁻, which is itself an oxidant.⁽⁴⁹⁾

If the molybdenum-99 is a fission product, the loss of ^{99m}Tc activity by adsorption is unimportant, except with very high activities of molybdenum.⁽⁵²⁾ On the other hand, if the molybdenum-99 is a reactor product the retention of technetium-99m by the column increases with increasing carrier molybdenum content.^(47, 48) This is now attributed to the semi-conductor properties of molybdenic oxide, MoO₃ (or its polymerized form).⁽⁵³⁾ Molybdenic oxide is an insulator which becomes a n-type semi-conductor by excitation, with an activation energy of 0.5 eV. The excitation is furnished by UV or X-ray photons, and presumably by beta particles as well. An electron-hole pair is created. The electron comes from a 2p orbital in an oxygen ion. Further excitation (3.2 eV) will move the electron to the conduction band of the molybdenum, where it is available for reaction with reducible species like pertechnetate. Oxygen is formed by the positive hole in a reaction with water. The oxides TiO₂ and WO₃, which are comparable to MoO₃, have been found to reduce cupric ions to copper metal when suspensions of the oxides in aqueous copper salt solutions are irradiated with ultraviolet light. Oxygen is simultaneously produced by the oxidation of water.^(54, 55, 56) In similar fashion, pertechnetate could be reduced to technetate by conduction-band electrons of the molybdenum, while oxygen is formed by the reaction of a positive hole with water. This interpretation means that the phenomenon of pertechnetate reduction is inherent in the carrier molybdate columns.⁽⁵¹⁾

Various remedies have been employed to correct this condition. In one form or another they involve adding oxidizing agents to the column^{32,37)} or adding scavengers of solvated electrons.¹⁵⁴⁾

The chemical condition of the eluate is important for labeling efficiency, especially when the pertechnetate is used with "instant" kits containing small amounts of stannous ion as the reducing agent. For large generators (> 2 Ci), Salehi and Guignard^{154a)} found that discarding the small volume of saline that remained in the dead volume below the column bed improved the binding efficiencies for radiolabeling platelets and lymphocytes with ^{99m}Tc. This experimental solution to low labeling yields did not address the mechanistic questions. The cause of the low yield could be attributed to the presence of decayed ^{99m}Tc as ⁹⁹Tc, peroxide due to radiolysis or disulfide compounds extracted from the rubber or plastic components.

Excess ⁹⁹Tc above the usual amount of stannous ion can be produced on Curie level generators.^{154b)} The total technetium concentration was determined using ion exchange HPLC with UV detection. For a 7 Ci generator, ⁹⁹Tc was present at 10⁻⁷ to 10⁻⁶M. The experimental values are higher than the theoretical values for ⁹⁹Tc by as much as 35%.

Srivastava et al.^{154c)} found that at low concentrations of stannous ion, reduction in DTPA kits was stoichiometric, but reduction in pyrophosphate kits was not, based on a 4 electron change in each. At <20 micrograms of tin(II), no improvement in the yield was seen after 4 hours of mixing and the reduction was substantially less than that calculated on the basis of the ⁹⁹Tc to tin(II) ratio. Various kits for the preparation of ^{99m}TcMAA gave very different labeling yields as a function of added ⁹⁹Tc, presumably because of different amount of "usable" stannous ion. Titration of the stannous ion content of various kits varied widely. In many modern "instant" kits, the amount of total stannous ion is small so that limitations on the ⁹⁹Tc content are recommended, e.g., for RBC^{154d)} and Ceretec.^{154e)}

Peroxide is the second possible oxidizing agent that could reduce the radiochemical yield. Molinski^{154f)} determined the yield of peroxide to be 0.33 ng/mCi/h and found microgram quantities of peroxide per mL eluate. This is generally too small to oxidize a substantial percentage of the stannous ion.

The final reducing agent suggested as a source of low radiochemical yields is the ill-defined group of rubber formation accelerators, which usually contains disulfide compounds. Hamilton found that µg/mL of sulfhydryl compounds could be extracted from rubber by solutions of iodinated contrast media.^{154g)}

Molinski^{154f)} reported that the presence of organic impurities reduced the elution yield, but it is possible that they also interfere with the labeling yield. Boyd and Sorby^{154h)} claimed that the vinyl sachet containing the saline in the so-called wet generators is a source of organic material. They increased the elution yields by purifying the saline eluent with charcoal, but did not comment on the effect of the purified eluate on radiochemical yields. In addition to plasticizers, they found cyclohexanone and propan-1-ol. Deutsch¹⁵⁴ⁱ⁾ also found compounds with strong UV absorption being eluted from one commercial generator. The low radiochemical yield is more prevalent for the initial elutions of the generator and more severe for the "wet" generators.^{154a, 154e)} The exact cause of the low radiochemical purity using the "Monday morning" generator is still unknown.

B. Instant Technetium

A second source of pertechnetate-99m is commonly called "instant technetium." A solution of Na₂MoO₄ containing molybdenum-99 is made strongly alkaline with NaOH (>2.5M) and is then extracted with a solvent like methyl ethyl ketone. The ketone is normally quite soluble in water at room temperature, but it is salted out by various concentrated electrolyte solutions. In strong alkali the molybdate remains in the aqueous phase, and sodium pertechnetate is extracted almost completely into the ketone. The organic solvent is then evaporated and the sodium pertechnetate is

dissolved in saline solution.⁽⁵⁹⁾ If this procedure is used on a large scale, it is necessary to add an oxidizing agent (air or H_2O_2 for example) to the aqueous solution in order to avoid the formation of an insoluble black material and to maintain the technetium in the heptavalent state. An additional problem arises from the inevitable reactions of ketones in strong alkali, yielding substituted mesityl oxides and other condensation products and possible pyrogens.⁽⁶⁰⁾ These are said to exert a deleterious effect on some labeling formulations.⁽⁶¹⁾

C. Sublimation Generator

A third source of pertechnetate-99m is a sublimation generator. Heating Mo/Tc mixtures causes sublimation of Tc_2O_7 which is much more volatile than MoO_3 . Such a generator has been reported to yield more than 50% of the theoretical activity from active MoO_3 which is heated to 850-890°C for a half-hour, with air flowing over it.⁽⁶²⁾ It is necessary to separate MoO_3 , which also sublimes to some extent, by decreasing the temperature by several hundred degrees in an intermediate trap in order to condense the MoO_3 . There are a number of other problems - including decreasing yields of Tc_2O_7 after repeated heatings - which have been solved in practice.⁽⁶³⁾

IV.

Technetium (VII) Compounds

A. General Chemistry of Tc (VII)

The lanthanide contraction causes the ionic radii of Tc and of Re to be very similar, and many of their compounds are isomorphous. The Tc-O distance in the tetrahedral TcO_4^- anion is 1.711 Å, and that of Re-O in ReO_4^- is 1.717 Å.⁽⁶³⁾ Perrhenate is reported to form very weak complexes with rare earth ions,⁽⁶⁴⁾ much weaker than those of chloride ion. The only reported pertechnetate complex is one with uranyl nitrate, determined qualitatively by extraction.⁽⁶⁵⁾ Perrhenate is different from pertechnetate in that it can form octahedral meso perrhenates in strong alkali;⁽⁶⁶⁾ which can react with certain polyhydroxy compounds containing 1,2 dihydroxy groups in the right configuration.⁽⁶⁷⁾ Another difference between perrhenate and pertechnetate is related to the probable formation of meso-perrhenate in weakly acid solutions of citrate and oxalate. Ordinarily perrhenate is difficult to reduce in water. Vajo and his collaborators reported that it was very easy to reduce it in citrate and oxalate media.^(68a) They attributed the facile reduction to the formation of complexes in which the perrhenate coordination number increased from 4 to 6. Citrate and other ligands were without effect on the polarographic reduction of pertechnetate in acid solution.^(68b)

Pertechnetate is very much like other oxo-anions such as perchlorate, ClO_4^- , in its solution behavior. Pertechnic acid, HTeO_4 , is described as a strong acid in aqueous acid base titrations. A recent estimate of its acid strength in water by osmotic coefficient measurement (which agree with Raman spectra) shows it, like HReO_4 and HClO_4 , to be completely dissociated even in 6M solutions.⁽⁶⁹⁾

It is a widely accepted idea in inorganic chemistry that salts of large anions and large cations are insoluble in water, and dissolve in various organic solvents. This is true of anions like ClO_4^- , ReO_4^- , and even I^- , which tend to precipitate with large quaternary ammonium, phosphonium or arsonium cations. The precipitates can then be extracted into water-immiscible solvents like benzene.^(70a,b) This is also true of both millimolar and nanomolar pertechnetate solutions. In addition, strongly basic anion-exchange resins in the chloride form will extract pertechnetate from water at all levels of concentration.^(71a,b) The resins are cross-linked quaternary ammonium compounds. Probably the type of interaction between quaternary ammonium salts and water, which is called "water-structure enforced ion-pairing", is responsible for the high selectivity of the resins towards pertechnetate.⁽⁷²⁾

B. Pertechnetate Binding To Proteins

Pertechnetate-99m in saline solution is injected intravenously into patients in a number of diagnostic procedures. Its condition in blood is not known. However, it is almost certainly bound to various proteins. Hays and Green reported that about 80% of $^{99\text{m}}\text{TcO}_4^-$ was bound to serum proteins at 37°C in a phosphate buffer at pH 7.4. Equilibrium dialysis was used to determine this; a lower value was obtained using gel chromatography.⁽⁷³⁾ The binding increased with decreasing temperature and increasing acidity. There was little difference between binding to normal serum and to 2.5 g% HSA

solution. The binding was assumed to be weak, since prolonged electrophoresis or prolonged dialysis resulted in the complete release of the pertechnetate from the protein(s).⁽⁷⁴⁾

A more quantitative estimate of the binding of pertechnetate to HSA was published by Kominami et al, using equilibrium dialysis at 20°C.⁽⁷⁵⁾ The pertechnetate concentration was varied from 10^{-3} M to 10^{-5} M; that of HSA was maintained at 10^{-5} M. The pH was varied from 7.38 to 0.65 by means of Tris, acetate and lactate buffers or with 0.4 M HCl for the more acid solutions. Scatchard plots were used to determine the association constant for the binding, as well as the number of sites:⁽⁷⁶⁾

$$\frac{\text{bound } \text{TcO}_4^- / \text{free } \text{TcO}_4^-}{\text{total HSA}} \quad \text{versus} \quad \frac{\text{bound } \text{TcO}_4^-}{\text{total HSA}}$$

Account was not taken of competition with chloride or buffer anions. From pH 7.38 to pH 5.10, the association constant increased from $1.42 \times 10^3 \text{ M}^{-1}$ to $2.25 \times 10^3 \text{ M}^{-1}$. The number of sites remained constant at 3. Calculation of the % bound $^{99\text{m}}\text{TcO}_4^-$ in physiological HSA (at 10^{-4} M) showed 64%. In a second paper the competition between TcO_4^- and either I^- or ClO_4^- for HSA binding was studied.⁽⁷⁷⁾ Both I^- and ClO_4^- individually had association constants of $1.00 \times 10^3 \text{ M}^{-1}$ with 3 binding sites (presumably the same) at pH 7.3. One conclusion of physiological interest was that the large release of $^{99\text{m}}\text{TcO}_4^-$ relative to blood plasma following the injection of KClO_4 was not due to the displacement of pertechnetate by perchlorate in blood, but rather due to the inhibition of TcO_4^- uptake in the thyroid and salivary glands in which the number of binding sites is limited. The overall results in this study were consistent with the earlier findings by Scatchard et al which were made for I^- binding using potentiometry.⁽⁷⁸⁾

Johannsen, Berger, and Schumacher investigated the binding of various technetium compounds, including pertechnetate, to HSA.⁽⁷⁹⁾ They used gel filtration and equilibrium dialysis. The latter measurements were carried out at 4, 20, and 37°C in pH 7.4 phosphate buffer and varying HSA concentrations, but at 10^{-9} M TcO_4^- . The binding constants were calculated on the assumption that one anion was bound to one HSA molecule. The binding equation is thus reduced to the radioimmunoassay formula:

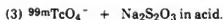
$$\frac{\text{Bound } \text{TcO}_4^-}{\text{Free } \text{TcO}_4^-} = K \times \text{total conc. of HSA}$$

At 20°C the constant was $6.1 \times 10^3 \text{ M}^{-1}$. One can calculate that at 20°C, their measurements showed that 75% of the pertechnetate is bound to HSA, compared to 64% in Kominami's work, and 80% from Hays' and Green's paper. This range is reasonable for low-affinity ligands studied at various concentrations of HSA. Dewanjee and his associates obtained similar results.⁽⁸⁰⁾

C. Technetium Sulfur Colloid - (Co-authored by Karen Linder)

Apart from pertechnetate itself, the only other Tc(VII) compound used in nuclear medicine is technetium heptasulfide, Tc_2S_7 . More accurately, the principal methods of preparation used in nuclear medicine yield Tc_2S_7 at higher levels of technetium concentration.^{81, 82} An undefined insoluble compound is used in colloidal form to measure liver perfusion by relative uptake in the reticuloendothelial cells, principally of the liver and spleen. There are three reported methods of making the preparation, which is called technetium sulfur colloid. They are:

- (1) $^{99\text{m}}\text{TcO}_4^- + \text{H}_2\text{S}$ in acid solution
- (2) $^{99\text{m}}\text{TcO}_4^- + \text{Sb}_2\text{S}_3$ colloid in acid, and

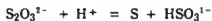


The first formulation of TcS-colloid in nuclear medicine was based on the reaction of ${}^{99m}\text{TcO}_4^-$ with H_2S in HCl solution.⁶³⁾ A technetium-containing colloidal dispersion of unknown, but very small particle size was produced, probably with some colloidal sulfur. The latter, if present, was formed by air oxidation of H_2S and the need to eliminate H_2S completely before injection led to technical complications.

The reaction of no-carrier-added TcO_4^- with previously prepared colloidal Sb_2S_3 was introduced into nuclear medicine in 1965.⁶⁴⁾ It is probably a surface reaction in which sulfide ions of the antimony compound are exchanged with oxide ions of the pertechnetate. This means that the final particle size will be determined by the size of the Sb_2S_3 colloid which can be made as small as several millimicrons in diameter. This is a well-studied colloidal system⁶⁵⁾ very much like As_2S_3 .⁶⁶⁾ There is, for example, an analytical procedure for various metals in which an exchange of oxide complexes is carried out on cellulose containing metallic sulfides like Ag_2S , CdS and As_2S_3 . Pertechnetate is one of the anions which undergoes sulfide formation on such treated papers in acid solution.^{67, 68)}

Until recently the major commercial source of colloidal technetium preparations was the Tc-S-colloid formed from pertechnetate-99m in an acidified solution of sodium thiosulfate.^{69, 70)} The addition of a perrhenate carrier does not change the basic chemistry discussed below. The reaction involves Tc(VII) for the most part. While thiosulfates are known to reduce pertechnetate to a limited extent under some conditions, a ${}^{99m}\text{Tc(IV)}$ compound added to a radiopharmaceutical preparation was not incorporated into the colloid.⁷¹⁾ Since high radiochemical yields are obtained with ${}^{99m}\text{Tc-S}$ -colloid, reduction must not be a serious problem.

Two types of thiosulfate reactions take place. There is first a reaction of thiosulfate with acid, forming sulfur and bisulfite:⁹²⁾

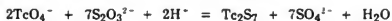
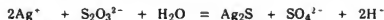


This is a complicated system in which polythionates are also formed:



In concentrated solutions of thiosulfate salts and strong acids, high-molecular-weight sulfur-oxygen polymers are also formed. The reaction rates, the nature of the reactions and the yields of the various products depend in a complicated way on thiosulfate concentration, acidity and temperature.

The second type of reaction of thiosulfates in the system of interest is an internal oxidation and reduction of thiosulfate in the presence of solutes which can form insoluble sulfides or stable sulfide complexes.^{93, 94)}



An acidified thiosulfate solution in which a metallic sulfide is formed will simultaneously generate sulfur, sulfite and polythionates. An investigation was carried out to

determine whether there was a connection between the two types of reactions, i.e., whether, for example, $^{99m}\text{Tc}_2\text{S}_7$ was forming on the surface of growing sulfur particles or was at the center.⁹³ A commercial Tc-S colloid kit was duplicated. The standard concentration of $\text{Na}_2\text{S}_2\text{O}_3$ was $5 \times 10^{-3}\text{M}$, and that of HCl was $5 \times 10^{-2}\text{M}$. $\text{Na}^{99m}\text{TcO}_4$ was added to 10^{-9}M , followed by gelatin, and the solution in a test tube was heated in a water-bath at 100°C for ten minutes. It was cooled, and the pH was raised to 6.5 with a phosphate buffer. Graded Nuclepore membranes showed that there was a range of particle sizes from 0.1 μm to 3.0 μm , resembling the average size found in three other commercial preparations.⁹⁶ Methods of analysis were developed for thiosulfate, sulfite and sulfur, and were applied to various Tc-S colloid preparations after Nuclepore membrane filtration. At the same time the thiosulfate and acid concentrations were varied, as was the incubation time at 100°C . The following Table shows some typical results in a 0.01 M $\text{Na}_2\text{S}_2\text{O}_3$ solution in which the other variables were "standard."

TABLE 1

Distribution of Tc in Nuclepore Filtrates-Particle Size (μm)

Particle Size, μm	%Tc	%S
> 1	5	8
1.0	7.5	10.5
0.6 - 0.4	73	80
0.4 - 0.1	1	1.5
< 0.1	13.5	0

In general, for particle sizes greater than 0.1 μm in diameter, the % of sulfur in the filtrates was not very different from that of technetium. However, for very small particles - those smaller than 0.1 μm , there was very little sulfur, but a significant yield of the technetium, of the order of 15%.

The analyses of Table I suggested that the Tc colloid was formed more rapidly than the sulfur colloid, and that the sulfur colloid formed at least in part on the Tc colloid which served as a nucleus. At the same time some sulfur nuclei were probably forming independently - that is, homogeneously. The classical work of Zaiser and LaMer showed that homogeneous nucleation of the sulfur colloid took place at room temperature in 0.001 - 0.002 M $\text{Na}_2\text{S}_2\text{O}_3$ and up to 0.002 M HCl .⁹⁷ When sulfur was generated in the thiosulfate-HCl solutions studied by LaMer, it was initially in homogeneous solution. As its concentration increased, it became supersaturated and at a certain degree of supersaturation, it suddenly formed nuclei which grew as more sulfur was homogeneously generated. The conditions of radiopharmaceutical preparation are not drastically different from those of his room-temperature studies. LaMer was interested in generating monodisperse sols and allowed the reaction to proceed only to the extent of 10%. The higher concentration of reagent, the higher temperature and the greater degree of conversion (about 60% of the available sulfur is in the elemental form in the standard preparation) produce a polydisperse sulfur colloid. The chemical similarity between the two types of experiments is shown in the yield of polythionate (determined by difference). It was 8-10% of total reacted sulfur for both the LaMer sols and the standard preparation.

In one experiment with a solution containing 10^{-12}M TcO_4^- in place of the 10^{-9}M concentration in the standard preparation, the distribution of radioactivity as a function of particle size was about the same in the two solutions. This suggested that other metal sulfides were acting as nuclei for the technetium in the more dilute solution, and perhaps in the standard solution as well. An analysis of two batches of reagent-grade $\text{Na}_2\text{S}_2\text{O}_3 \cdot 5\text{H}_2\text{O}$ showed a total of 1.2 ppm of Ag, Cu, Sb, and Sn and more than 1 ppm of W in each. Undoubtedly, gelatin and HCl also contain metal salts which

can form sulfides or sulfide complexes by reacting with thiosulfate in acid. The total concentration of such metals may be variable from batch to batch, but they may be in excess relative to the technetium. If they form sulfides more quickly than technetium, they may carry the latter by sulfide-oxide exchange.

Since the publication of the first article on Tc-S-colloid⁸³⁾ it has been the practice in the field to raise the pH of a cooled colloid preparation to 6 or 6.5, but no higher. It was reported that in more alkaline solutions Tc_2S_7 hydrolyzes back to pertechnetate. If the mechanism of particle formation described earlier is operative, it should be possible to dissolve away the sulfur enclosing the nuclei of metallic sulfide simply by raising the pH. Sulfites attack sulfur, reversing the thiosulfate decomposition in acid:



This reaction should take place readily above pH 8 if sulfite is the active ingredient ($\text{pK}_1 = 1.81$, $\text{pK}_2 = 6.91$).⁹⁸⁾ Even at pH 6.5 some 30% of the total bisulfite should be in the sulfite form. There is already one demonstration of this (without explanation) in the nuclear medicine literature. A letter described a 2-minute reheating of Tc-S-colloid preparations whose average particle size was greater than 1 micron.⁹⁹⁾ This second heating - which undoubtedly dissolved some of the sulfur - produced a clear dispersion.

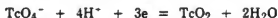
The redissolution of Tc_2S_7 in alkali to reform TcO_4^- is a matter of both equilibria and kinetics. If KTcO_4 is dissolved in 1 M KOH, and H_2S is passed into the solution, Tc_2S_7 is quantitatively precipitated after 24 hours.¹⁰⁰⁾ This means that with enough sulfide ion present, Tc_2S_7 is insoluble even in a strongly alkaline solution. If there is insufficient sulfide in solution, Tc_2S_7 might dissolve in alkali. At this point, the rate of attack of alkali on the metal sulfide becomes important. In a series of experiments the standard TcS-colloid preparation described above was made alkaline to pH 10.5 and heated at 100°C for ten minutes. The percentage of colloid which passed through a 0.1 micron Nucleopore filter was 10-20% in the standard preparation. This was raised to 90-100% with the reheating of the now-alkaline solution. In addition, an increase in the gelatin concentration or the use of 5% HSA further reduced the particle size to that undefinable point at which almost all the activity emerged in the void volume of a G-25 Sephadex column.

In summary, Tc_2S_7 is formed rapidly from acidified thiosulfate solutions at 100°C, directly and by reaction with other metal or metalloid sulfides (the latter arising from impurities in the reagents). Sulfur is formed independently by homogeneous nucleation and by condensation from supersaturated solution on the Tc_2S_7 nuclei. The sulfur can be dissolved by heating the colloidal dispersion in mild alkaline solution, reforming thiosulfate from the sulfite which is present and leaving extremely small colloidal particles carrying the technetium.

D. The Reduction Potential of Technetium (VII)

This section describes the reduction potential of pertechnetate, the chemistry of a number of reducing agents, and the chemistry of different oxidation states of technetium.

The equilibrium electrochemistry of pertechnetate in water is limited to the $^{99}\text{TcO}_4^-$ - $^{99}\text{TcO}_2$ couple:



Cartledge and Smith reported that the standard reduction potential was +0.738 volts vs. the normal hydrogen electrode (NHE) at 25°C,¹⁰¹⁾ correcting an earlier value by Cobble, Smith and Boyd,¹⁰²⁾ whose cell contained air. Muenze found a small variation of potential with pH.¹⁰³⁾ Spitsyn et al found E_0 to be 0.710 volts,¹⁰⁴⁾ but the concentration of pertechnetate was too low: it was less than $3 \times 10^{-5}\text{M}$, and hence the system may not have been in equilibrium. The standard reduction potential of

pertechnetate is higher than that of perrhenate ($E_0 = 0.510\text{V}$), but very much lower than that of permanganate (1.695V).¹⁰⁶ It is a stable species in water.

Standard potentials of other couples which are in the literature are derived from the measured TcO_4^- - TcO_2 couple and various free energy functions which in turn are based on enthalpy measurements and entropy calculations.¹⁰⁶ Table II lists several of these.

TABLE II

STANDARD ELECTRODE POTENTIALS FOR TECHNETIUM

Half-Reaction							Standard or Formal Potential, Volts
TcO ₄ ⁻ (aq)	+	2H ⁺	+	e ⁻	--->	TcO ₃ (S) + H ₂ O	+0.700
TcO ₃ (S)	+	2H ⁺	+	2e ⁻	--->	TcO ₂ (S) + H ₂ O	+0.757
TcO ₂ (S)	+	4H ⁺	+	4e ⁻	--->	Tc ²⁺ + 2H ₂ O	+0.144
TcO ₂ (S)	+	4H ⁺	+	4e ⁻	--->	Tc(S) + 2H ₂ O	+0.272
TcO ₄ ⁻ (aq)	+	8H ⁺	+	7e ⁻	--->	Tc(S) + 4H ₂ O	+0.472

The electrode reaction is extremely sluggish, and requires hours for equilibration for millimolar solutions.

V.

The Chemistry of Various Reducing Agents Used with Pertechnetate

A. $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$

This reagent is the most widely used reductant for pertechnetate in radiopharmaceutical practice. Because it is present in kits in large excess relative to pertechnetate, it maintains a reducing presence in solutions prior to injection. It is difficult to obtain as a pure compound, free of tin (IV). Commercial grades of $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ may contain more than 5% of Sn(IV) ⁽¹⁰⁷⁾ and there is some evidence that auto-oxidation occurs in the solid state.⁽¹⁰⁸⁾ Solid SnSO_4 ⁽¹⁰⁷⁾ and solid Sn(II)acetate ⁽¹⁰⁹⁾ are much more stable than the chloride, and can be maintained in a pure state.

Tobias investigated the equilibria of stannous perchlorate in 3M sodium perchlorate solutions at various acidities.⁽¹¹⁰⁾ He found that Sn^{2+} ions existed in these solutions, that they hydrolyzed even in acid, that they hydrolyzed to cyclic complexes - $\text{Sn}_3(\text{OH})_4^{2+}$ or $\text{Sn}_2\text{O}(\text{OH})_2^{2+}$, and that they formed soluble $\text{Sn}(\text{OH})_3^-$ in alkali. The main ions in solution before precipitation of the hydroxide are: $\text{Sn}(\text{OH})^{1+}$, $\text{Sn}_2(\text{OH})_2^{2+}$, and the predominant species, $\text{Sn}_3(\text{OH})_4^{2+}$. The addition of chloride ions to stannous perchlorate - perchloric acid solutions produced additional complexes. Formation constants at 25°C were determined for $\text{Sn}(\text{OH})^+$, for a mixed chloro-hydroxy tin complex, and for SnCl^+ , SnCl_2 and SnCl_3^- .⁽¹¹¹⁾ The successive formation constants for the latter three complexes were approximately 14, 3.6 and 0.97M^{-1} .

A recent determination of these constants showed essentially the same values.⁽¹¹²⁾ A basic salt was isolated from chloride-containing solutions below pH 4.5. Its composition is $\text{Sn}_4(\text{OH})_6\text{Cl}_2$.⁽¹¹³⁾ Above pH 4.5 mixtures of various solids were obtained. Above pH 5.5 colloidal tin species are formed before the hydroxide precipitates. The latter is not a true hydroxide, but is an amorphous hydrous oxide whose composition is $\text{Sn}_5\text{O}_3(\text{OH})_4$ (formed at pH 10 from SnSO_4 solutions).⁽¹¹⁴⁾

It may be concluded that in radiopharmaceutical preparations (which are always made in saline solution) there will be very few Sn^{2+} ions, probably some chloro complexes, some polymers (in the absence of ligands which can complex Sn(II)) and some colloidal tin aggregates. Hence, to describe the real reducing agent as Sn^{2+} is incorrect, and to describe it as SnCl_2 or SnCl_3^- in saline solutions may be only partly correct.

The standard reduction potential of the Sn(IV)-Sn(II) couple in HCl is +0.15 volts versus the standard $\text{H}^+ - \text{H}_2$ electrode at 25°C.⁽¹¹⁵⁾ The inevitable presence of Sn(IV) as an impurity in commercial solid $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ will lower the potential in solution to 0.11-0.12 volts. In the presence of excess chloride it will be closer to 0 volts.⁽¹¹⁶⁾ The measurement of the equilibrium potential of tin salts in aqueous solution is difficult. The couple is not reversible on solid electrodes.⁽¹¹⁷⁾ It will come to equilibrium in hours on mercury electrodes⁽¹¹⁸⁾ and this has led to the use of tin amalgam electrodes for potentiometric measurements.⁽¹¹¹⁾ In alkaline solutions the $\text{Sn}(\text{OH})_3^-$ complex is formed, and the stannate-stannite couple becomes more powerful as a reductant by more than a volt, compared to acid

solutions.¹¹⁵ In the presence of added ligands which may complex either Sn(II) or Sn(IV) or both, the reduction potential of the couple will depend on the relative formation constants of the tin complexes.

The mechanism of reduction by Sn(II) compounds has been described in terms of complementary and non-complementary reactions. In complementary reactions the same number of electrons is given up by the reductant and taken up by the oxidant.¹¹⁹ The following case describes a complementary two-electron transfer:



Such transfer reactions are usually quite rapid. On the other hand, when the same number of electrons is not exchanged by the two reactants, the chemistry becomes more complicated. In the reduction of Fe(III) by Sn(II), the reaction is non-complementary:



This is a slow reaction at room temperature. The original explanation for the slowness of such reactions - that a three-body collision is required¹²⁰ - has long been discarded. What has been suggested for some of these Sn(II) reductions is the formation of an unstable oxidation state of tin, Sn(III). Its formation would make possible two successive one-electron-transfer steps:¹²¹



Sn(III) in solution has been produced by the flash photolysis of Sn(II) or Sn(IV) chlorides in deaerated HCl solutions.¹²² It has a very short half-life. Its concentration in a redox reaction will be very small, and this can account for the slowness of those non-complementary reactions where its presence has been hypothesized. Higginson and his collaborators have concluded from kinetic studies and studies of the reactions of an added Co(III) indicator complex that Sn(III) is an intermediate in some reductions (Ce(IV), Fe(III), Cr(VI) and Mn(VII)), but is absent in others (H₂O₂, I₂, Br₂, Ti(III) and Hg(II)).^{123,124,125} The latter group of redox reactions are complementary two-electron reactions.

A more far-reaching analysis of the nature of electron transfer systems comes from their examination as outer-sphere or inner-sphere reactions. The simpler electron-transfer reactions are called outer-sphere; in these, each complex retains its own full coordination shell, and the electron passes through both. Reactions in which the two reactants form an intermediate in which one or more ligands are shared are called inner-sphere or ligand-bridged reactions.¹²⁶ In at least one reduction by Sn(II) there is probably an inner sphere mechanism operating. The slow reduction of Fe(III) by Sn(II) is catalyzed by chloride ions, and an analysis of the kinetics of the reaction shows that the chloride-ion concentration enters as the fourth power in the rate-determining step (and at high chloride concentrations as the fifth power).¹²⁷ The reaction is not speeded up even if the tin is added as SnCl₂; chloride beyond this 2:1 ratio (Cl:Sn) is needed for the acceleration. These results suggest that the complex SnCl₃⁻ is reacting with a Fe(III) chloro complex (accounting for the fourth-power dependence of the chloride-ion concentration) and that a chlorine atom is transferred from the Fe(III) coordination sphere to that of the tin. This will produce Fe(II) and a hypothetical (Sn(III)Cl₄)¹⁺.

There are several reports in the literature which state that SnCl₃⁻ is the most reactive reducing form of Sn(II). In a kinetic study of the reaction between Sn(II) compounds and methyl orange in water, Duke and Peterson observed that there was no reaction in the absence of chloride, and that SnCl₃⁻ was the principal tin reagent.¹²⁸ A similar finding was reported by Haight and von Frankenberg for the reduction of hydroxylamine by Sn(II), catalyzed by molybdate. The most reactive form of tin was SnCl₃⁻, but the reaction in the absence of molybdate did not proceed.¹²⁹ In these cases, it is possible that an inner-sphere complex is formed with the lone pair of electrons at the apex of pyramidal SnCl₃⁻ and nitrogen atoms and oxygen atoms respectively.

At the present time, it is not possible to decide whether the SnCl_3^- species will be formed in radiopharmaceutical preparations to the exclusion of hydrolyzed and polymerized Sn(II) species, since this will depend on the pH of the particular preparation, and the degree of dilution of the saline solution which is commonly used for the elution of $^{99\text{m}}\text{Tc}$ pertechnetate in the generators. The view held by the authors is that complementary reactions between pertechnetate and compounds of Sn(II) will be more rapid than the non-complementary reactions. Thus, the reduction of Tc(VII) to Tc(V) by Sn(II) will be more rapid than the reduction of Tc(V) to Tc(IV) . In this connection, inner-sphere reactions in the reduction of pertechnetate by Sn(II) , may proceed by way of the following oxygen transfer :



This would be a complementary reaction.

The possibility of the formation of mixed tin-technetium complexes is often raised. The usual coordination of Sn(IV) to transition metals is by metal-to-metal bonding with covalent bonds.¹³⁰¹ SnCl_3^- acting as a ligand is known to form complexes with platinum metal halides in which there is a metal to metal bond.¹³¹¹ These show very strong color changes on formation. With respect to technetium compounds, there is little evidence of widespread tin-technetium mixed-metal complexes. A Tc-Sn mixed complex is reported by Deutsch et al in which the critical bond is an oxygen bridge between Tc and Sn.¹³²¹ This compound, a dimethylglyoxime complex, has been characterized by its X-ray diffraction pattern. A second reported complex - a Sn(II) - Tc(III) - Tc(IV) - phosphate complex of unknown composition - was indirectly shown to exist by Steigman et al.¹³³¹ Hydroxyethylidene diphosphonate (HEDP) has been reported to form mixed-metal complexes with Sn(II) and reduced technetium.^{134,1351} The latter claim was based on low-performance polyamide chromatography. However, recent investigation of the system employing HPLC spectrophotometry and double isotope labeling showed that there was no detectable tin in the four to five main HEDP complexes and only one of 13 minor complexes contained the tin isotope.¹³⁶¹

On the other hand, no mixed-metal complex was found in the Tc-HIDA complexes,¹³⁷¹ in the Tc-pyrophosphate complex,¹³³¹ or in the Tc-gluconate complex.¹³⁸¹ In the latter two cases, SnCl_2 reduction and another method of reduction in the presence of the appropriate ligand yielded identical spectra of the technetium complexes.

It is possible that hydroxy-acids may form mixed-metal complexes. Sn(II) does form chelates with citric and tartaric acids, and these chelates do interact with some transition metals.¹³⁹¹ Fe(III) and Cu(II) will form 1:1:1 complexes with Sn(II) and citrate. Such complexes do not form with Ni(II) , Cu(II) , Al(III) , Th(IV) , U(VI) , Mn(III) or Fe(II) . In the opinion of the investigator,¹³⁹¹ it is necessary for the transition metal ion to be easily reducible, which points to the possibility of an internal oxidation-reduction reaction in the mixed complex, forming, say, Fe(II) - Sn(III) . If this is the driving force of the mixed citrate complexes, technetium in some state may indeed behave like Fe(III) . However, no such mixed-metal complex has yet been reported.

It cannot be taken as a general rule that Sn(II) will tend to form mixed-metal complexes with technetium compounds. On the contrary, the evidence is scanty that such complexes do form. Each technetium compound produced by reduction with SnCl_2 must be evaluated separately in this regard.

B Sodium Borohydride

Sodium borohydride, NaBH_4 was introduced into nuclear medicine by Subramanian and McAfee.¹⁴⁰¹ It is a commonly used reducing agent in organic synthesis. It is regarded by organic chemists as "mild" in its reducing action compared, say, to LiAlH_4 .¹⁴¹¹

It undergoes two types of reactions with inorganic compounds in aqueous solution. First, it reacts rapidly with first-row transition metals in alkaline solution, producing borides like Co_2B and Mn_2B .⁽¹⁴²⁾ The addition of more NaOH does not alter the reaction. Some of these borides (Fe , Co , Ni) have been found to reduce pertechnetate 99m, but the radioactivity is largely associated with the insoluble boride.⁽¹⁴³⁾ Secondly, it reduces various inorganic compounds, slowly in basic solution and much more rapidly in acid. The reaction of borohydride anions with aqueous acids is reported to be a general acid-catalyzed reaction in which the anions are capable of reacting with H_3O^+ and also with H_2O and other Brønsted acids.⁽¹⁴⁴⁾ There is general agreement that the reaction with hydronium ions proceeds as follows:^(144,145)



The non-classical BH_5 particle, whose coordination resembles that of the non-classical CH_5^+ carbocation,⁽¹⁴⁶⁾ has been postulated on the basis of various exchange experiments with deuterium compounds; the CH_5^+ particle has been observed in mass spectroscopic studies.^(147,148)

Borane BH_3 and its dimer, B_2H_6 , undergo virtually instant hydrolysis in water, forming boric acid and hydrogen. It is highly probable in borohydride reductions in water that most of the borane and diborane are hydrolyzed, but that they are the effective reducing agents for pertechnetate. The other product - hydrogen gas - is generally an ineffective reductant in the absence of a catalyst.

Pacer found that acidified NaBH_4 reduced perrhenate to a mixture, which included rhenium metal and/or adsorbed hydrogen.^(149,150) A similar experiment with pertechnetate, in which the pertechnetate-borohydride mixture was acidified dropwise with 1 M acetic acid, at first produced a pink color. On continued addition of acid, the solution darkened, and deposited a black solid which was largely technetium metal. The electron number, n , of the pertechnetate in this reaction was 7.7. The excess (0.7) was attributed to traces of unreacted BH_4 compounds. An additional finding of analytical interest was that the black metal reacted rapidly with a ceric salt solution, but an intermediate product was oxidized very slowly to Tc(VII) .

From this investigation, it would appear that caution must be applied in the use of NaBH_4 in order to avoid the reduction of pertechnetate to a lower oxidation state than the desired one. In the experience of one of us, the reduction of $\text{NH}_4^{99}\text{TcO}_4$ by NaBH_4 in the presence of mannitol yields either the pink Tc(V) complex which is described later or a black dispersion. The latter is produced by higher concentrations of borohydride and acid, and represents reduction to TcO_2 .⁽¹⁵¹⁾

In one reported case, the production of a lower oxidation state by borohydride reduction of pertechnetate offered an advantage. A dihydrothioctic acid complex of technetium (a 6-membered-ring dithiol complex) did not exchange with 1, 2-dimercaptopropane when the complex was prepared using SnCl_2 as the reductant. Exchange was rapid when NaBH_4 was the reductant. Burns and his collaborators attributed the difference to the production of traces of a labile technetium complex in a lower oxidation state and recalled the use of cobalt (II) compounds which catalyze ligand exchange reactions of sluggish cobalt (III) complexes.⁽¹⁵²⁾

C. Sodium Dithionite

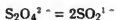
$\text{Na}_2\text{S}_2\text{O}_4$ is an extremely powerful reducing agent, particularly in alkaline solution.⁽¹⁵³⁾ In acid solution, it decomposes to thiosulfate and bisulfite:



The standard reduction potential (versus the normal hydrogen electrode) is given as -1.12 volts for the half-cell reaction.



Its reducing ability is attributed to the sulfoxylate ion-radical formed by dissociation:



It can reduce many metallic salts to lower oxidation states or to the metal. It was found to be an effective reagent in the pH range 11-13 for reducing TeO_4^{-1} to $(\text{TeO}(\text{SCH}_2\text{CH}_2\text{S})_2)^{-1}$ in the presence of ethanedithiol.⁽¹⁵⁴⁾

D. Hypophosphorous Acid

Hypophosphorous Acid, H_3PO_2 , is an extremely powerful reducing agent in both acid and alkaline solution.⁽¹⁵⁵⁾ The reduction potential at 25°C in acid is -0.50 volts and in alkaline solution is -1.57 volts:



These are calculated from free energy relationships.⁽¹⁵⁵⁾

The rate of H_3PO_2 reductions in acid solution is independent of the type or concentration of the oxidant, leading to the conclusion that the rate-determining step in these reactions is the conversion of the normal form of H_3PO_2 to an active form.⁽¹⁵⁶⁾

Hypophosphorous acid has been used as a reductant in concentrated HCl for the synthesis of quaternary ammonium salts of the TeOCl_4^{-1} anion.⁽¹⁵⁷⁾ Earlier work done on solutions⁽¹⁵⁸⁾, and followed by crystal analysis⁽¹⁵⁹⁾ was confirmed. A report that H_3PO_2 in concentrated HCl produced $\text{Te}_2\text{Cl}_8^{2-}$ ⁽¹⁶⁰⁾ was not confirmed.⁽¹⁶¹⁾

E. Hydrazine

Hydrazine, NH_2NH_2 , is both an oxidizing and a reducing agent. In alkaline solution it is a powerful reductant. The standard reduction potential at 25°C, calculated from free energy data, is -1.16 volts.⁽¹⁶²⁾



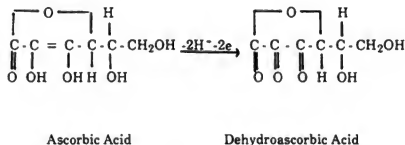
It may produce NH_3 and HN_3 in addition to N_2 . The oxidation of hydrazine probably proceeds in steps, perhaps by way of free radicals. Its oxidation by Ce(IV) in dilute acid was studied by EPR in a stopped-flow apparatus. The EPR spectrum was assigned to $\text{N}_2\text{H}_4^{\cdot +}$, an ion-radical.⁽¹⁶³⁾ This means that in acid solution hydrazine is capable of transferring a single electron to an oxidant. It is also capable of forming diimine:



This product is found in reactions of hydrazine with 2-electron oxidants.

F. Ascorbic Acid

Ascorbic acid, $C_6H_8O_6$, has been used alone or with a ferrous or ferric salt, as a reducing agent in radiopharmaceuticals. The structural formulae of the acid and of its immediate oxidation product, dehydroascorbic acid, are shown in the following equation:



This equation describes the reversible behavior of the redox couple from more acid solutions to pH 4. Above this pH, there is an irreversible change in the dehydroascorbic acid which becomes more marked in increasingly alkaline solution, and involves the formation of 2,3-diketogulonate.^[164] Any measured reduction potential is meaningless in the absence of suitable catalysts. By itself the redox system is sluggish in its response to electrodes.^[165] The properly catalyzed or mediated redox couple has a standard reduction potential at 25°C of about +0.33 volts at pH 1 (relative to the normal hydrogen potential). This decreases to +0.18 volts at pH 4, and to almost zero at pH 8.

Ascorbic acid shows two dissociation constants in water at 25°C: K_1 is 9.16×10^{-5} and $K_2 = 4.57 \times 10^{-12}$.^[166] This means that the ascorbate mono-anion will be the principal reactant in redox operations in moderately acid to moderately alkaline solutions.

It is generally accepted that the acid (or mono-anion) is oxidized to a free radical in a 1-electron-transfer step, the electron originating in one of the two hydroxyl groups on the two ethylenic carbon atoms. It was originally hypothesized that the radical lost an electron in a second step, forming dehydroascorbic acid. This was in accord with the Michaelis mechanism in which a two-electron redox reaction takes place in two successive one-electron-transfer steps, with a free radical as an intermediate.^[167] However, it has been shown more recently that dehydroascorbate is not formed in two successive electron-transfer steps, but that it is one of the two products of disproportionation of the ion-radical. If H_2A stands for ascorbic acid, HA^- represents the ascorbate mono-anion, $\bullet HA^-$, the ion-radical, and A the dehydroascorbic acid, then:

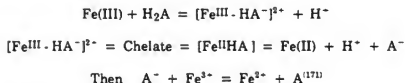


Ascorbic acid or the mono-anion is a reductant. The ion-radical, produced by various techniques including electron bombardment of solutions of the acid, is not a very good reductant. In fact, in acid solution it behaves like an oxidant. Its standard reduction potential at room temperature is +0.99 volt at pH 0 (where it is generally an oxidant), decreasing to 0.3 volt at pH 7, and to less than 0.1 volt at pH 11 (where it is a reductant).^[169] The radical is a moderately strong acid with an estimated $pK_A =$

-0.45. A study of solutions of the radical produced in various ways showed a single species to be present from pH 0 to pH 13.⁽¹⁷⁰⁾ The kinetics of radical disproportionation showed a rapid reaction ($k = 10^6 \text{M}^{-1} \text{s}^{-1}$) to pH 5 or so, and a marked decrease at pH 8-11 ($k = 4 \times 10^4 \text{M}^{-1} \text{s}^{-1}$).

The reaction rate of ascorbate with molecular oxygen is slow, and is pH dependent. It is a complicated reaction whose mechanism is not clear. It may involve the direct reaction of O_2 with ascorbate to form dehydroascorbic acid and H_2O_2 , or the formation of the superoxide radical O_2^- and the ion-radical. The latter is known to be formed in the auto-oxidation of ascorbic acid.⁽¹⁶⁸⁾

Ferric salts and copper(II) salts catalyze the auto-oxidation of ascorbic acid, although not necessarily by the same mechanism.⁽¹⁷¹⁾ A stopped-flow study of the reaction of a ferric salt with ascorbic acid in a degassed solution showed that there was a transient complex with a rather short half-life (about 500 ms for $2.5 \times 10^{-2} \text{M}$ solutions) and with a deep purple color (maximum absorption near 560nm). The reaction kinetics suggested that the reaction was not a simple one-step process, and the authors suggested the following sequence:



The last step - the reduction - would take place to a greater extent at high pH.

Yokoyama and his collaborators produced the purple complex in ascorbic acid solutions by adding ferrous salts, and exposing the mixture to air.⁽¹⁷²⁾ They attributed the purple color to a cationic Fe(II) complex which ultimately hydrolyzed to Fe(OH)_3 as the pH was raised. They pointed out that the iron-ascorbate system was far more effective than ascorbic acid alone in labeling albumin with non-carrier-added technetium.

There are many reports in the chemical literature of vinyl polymerizations which are initiated by Fe(III) -ascorbate mixtures, like similar polymerizations initiated by Fenton's reagent ($\text{Fe(III)} - \text{H}_2\text{O}_2$ mixtures). Presumably the initiation is due to the ascorbate free radical, although it may be due to hydroxyl radicals generated by reactions with dissolved oxygen. In this connection, one of the early methods of labeling albumin with technetium was based on a $\text{Fe(III)} - \text{ascorbate}$ reduction of pertechnetate in the presence of air.⁽¹⁷³⁾ It is possible that the labeling was accompanied by some breakdown of the protein, an effect which was quite evident in the reactions of albumin with $\text{Cu(II)} - \text{ascorbate}$.⁽¹⁷⁴⁾

G. Sulfhydryl (and related) Compounds

The standard reduction potentials of sulfhydryl compounds like cysteine are difficult to measure. The reactions at electrode surfaces are sluggish, and electrode poisoning (like that caused by H_2S) has been found. The difficulties in such measurements are described in detail in Clark's monograph.⁽¹⁷⁵⁾ The generalized reaction is:



For the cysteine-cystine couple, the potential is calculated from free energy changes which in turn are calculated from thermal and supplementary data (including assigned, but not proven dissociation constants). The calculated standard reduction potential at 37°C is $+0.03$ volts at pH 0, and -0.40 volts at pH 7. Some of the measured potentials are not far from these values. Polarographic

measurements have been made, but these may reflect the half-wave potentials for the oxidation of mercury and the formation of the Hg(II)-sulfhydryde complex. Thiourea, $(\text{NH}_2)_2\text{C} = \text{S}$, and its oxidized product, formamidine disulfide, have been studied in acid. The reaction is:

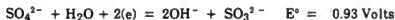


The recorded standard reduction potential is +0.418 volts in 1N H_2SO_4 at 30°C. The disulfide is unstable in solutions whose pH is greater than 5. No mechanism has been formulated for this reaction.

The mechanism of reduction by thiols like cysteine is complicated. The reaction between Ce(IV) and cysteine in acid solution proceeds by way of the formation of thiol free radicals ($\text{RS}\cdot$) in a 1-electron-transfer reaction, but may produce further oxidized free radicals like $\text{RSO}\cdot$ and $\text{RSO}_2\cdot$.⁽¹⁷⁶⁾ There is some disagreement about the further steps. It has been maintained that the oxidation of cysteine produces only $\text{RS}\cdot$ and $\text{RO}\cdot$ radicals.⁽¹⁷⁷⁾ In any event, the first step in reductions by simple mercaptans would appear to be a one-electron-transfer step, yielding a free radical.

H. Sulfur Dioxide

Sulfur dioxide has been used to reduce pertechnetate. The standard reduction potentials have been calculated from thermodynamic data for the two reactions:^(178, 179)



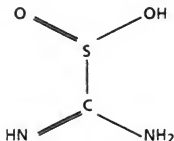
Sulfite (as sulfurous acid), SO_2 or bisulfite can react with 1-electron-transfer oxidants like Fe(III) to give SO_3^{1-} (actually the dimer dithionate, $\text{S}_2\text{O}_6^{2-}$) as well as sulfate, and with two-electron-transfer oxidants like halogens to give sulfate alone.⁽¹⁸⁰⁾ In general, reactions of sulfite ions with oxidants like chlorate, appear to involve oxygen atom transfer.⁽¹⁸¹⁾ With oxygen-18-labeled chlorate, it was established that the oxygen atom came from the chlorate.⁽¹⁷⁶⁾ It is likely that the reduction of pertechnetate by a sulfite or bisulfite anion also involves the direct transfer of an oxygen atom (as an oxide ion).

I. Hydrochloric Acid

HCl occupies a special place in the group of reagents which have been used to reduce pertechnetate. Concentrated HCl produces two starting materials which have been used in substitution reactions with various ligands, salts of the TcOCl_4^{1-} anion for Tc(V) compounds, and salts of the TcCl_6^{2-} anion for Tc(IV) compounds. The corresponding bromo compounds are often preferred because of their higher reactivity. Pertechnetate reacts with HCl at room temperature. A transient yellow color develops which is believed to be a Tc(VII) chloro-addition product, *fac* $\text{TcO}_3\text{Cl}_3^{2-}$,⁽¹⁸²⁾ by analogy with a Re(VII) chloro-addition product whose cesium salt was isolated.⁽¹⁸³⁾ The yellow product was temporarily stabilized in concentrated choline chloride solution (in HCl), its spectrum was recorded, and it formed a Tc(VII) complex with dipyriddy. ^(184, 182) In concentrated HCl, this transient yellow species is rapidly transformed to the green Tc(V) complex, TcOCl_4^{1-} , and chlorine. On heating in concentrated HCl, the TcOCl_4^{1-} is further reduced to the Tc(IV) complex anion, TcCl_6^{2-} .

J. Formamidine Sulfinic Acid

Formamidine sulfinic acid, also known as aminoimino-methanesulfinic acid and thiourea dioxide, has

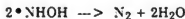


been used as a substitute for stannous salts in the preparation of a number of technetium-99m-tagged radiopharmaceuticals.⁽¹⁸⁵⁾ The reduction potential and the rate of change of potential with conditions are complicated functions of the solution composition, the pH, temperature, and reductant concentration. Among other things, it liberates SO_2 at elevated temperatures. In acid solution, it is more likely to behave as a ligand than as a reductant. In neutral solution, it will reduce U(VI) to U(IV) with boiling,⁽¹⁸⁶⁾ but will reduce various biochemically important compounds like cytochrome C and ferredoxin at room temperature.⁽¹⁸⁷⁾ In alkali, where it is a powerful reductant, it undergoes complicated decomposition reactions. Urea is formed, and electron-spin measurements showed that dithionite is present since the SO_2^- radical ion was found. However, its reducing ability is not due to dithionite alone. Hydrogen is liberated from these alkaline solutions, and Cd(II) is reduced to the metal. Dithionite is not capable of these reductions. It was hypothesized that there was homolytic scission of the C-S bond in the parent molecule, forming SO_2 and a carbon-containing free radical ion which was a more powerful reducing agent than dithionite. This was suggested in part because the cadmium metal contained carbon, which could not have come from the dithionite.⁽¹⁸⁶⁾ In this same work, it was concluded that the reduction potential of the compound was between -0.809 volts (the Cd-reduction potential)⁽¹⁸⁸⁾ and -1.245 volts (the zinc reduction potential),⁽¹⁸⁹⁾ since zinc metal was not formed, whereas Cd metal did form.

K. Hydroxylamine

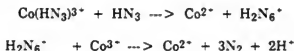
Hydroxylamine, NH_2OH , which is better known as a ligand in various metal-ion complexes, can act as either an oxidant or a reductant. Qualitatively, its reactions as a reductant are complicated: Ag(II) and Mn(III) oxidized it to NO_3^- , Ce(IV), Ag^+ , Cu(II), $\text{Fe}(\text{CN})_6^{3-}$, Cr(VI) and Fe(III) oxidized it to N_2 , to N_2O , or to a mixture. Co(III) will oxidize it to NO_2^{1-} .⁽¹⁹⁰⁾

Pulsed radiolysis studies led to the conclusion that NH_2OH on oxidation by OH radicals formed $\bullet\text{NHOH}$ radicals, which decayed by a second-order dimerization:⁽¹⁹¹⁾

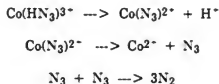


In a study of the reaction of hydroxylamine with Ce(IV), it was hypothesized that an $\text{NH}_2\text{O}\bullet$ radical was formed, which could react with a second Ce(IV) ion to form NHO and the latter could react further.⁽¹⁹²⁾

Hydrazoic acid, HN_3 , like hydroxylamine and hydrazine can function as either an oxidant or a reductant. In the latter case, the product is usually nitrogen, formed perhaps by the dimerization of a free radical. Thus, in the oxidation of HN_3 by Co(III) , two reactions have been proposed, depending on the $\text{HN}_3/\text{Co(III)}$ ratio. At a high ratio:



At low $\text{HN}_3/\text{Co(III)}$ ratios:⁽¹⁹³⁾



Similar mechanisms have been advanced for a Ni(III) reduction.⁽¹⁹⁴⁾

L. Solid or Second-Phase Reductants

Solid-phase reductants for pertechnetate -99m have been developed by a number of investigators, usually for the purpose of reducing the Sn(II) content of the radiopharmaceutical preparation or for eliminating the use of SnCl_2 or other soluble Sn(II) compound entirely. One such method utilized insoluble Sn(II) salts: $\text{Sn}_2\text{Fe(CN)}_6$, $\text{Sn}_3[\text{Fe(CN)}_6]_2$, SnS or SnSe . These were added to a sodium phytate solution, and lyophilized. They were subsequently homogenized with pertechnetate -99m solution and filtered.⁽¹⁹⁵⁾

Sn(II) -saturated chelating resins were used for the same purpose. An early paper described the use of Sn(II) -Biorad Chelex.⁽¹⁹⁶⁾ A later paper included EDTA or oxine covalently bonded to controlled pore glass beads, and Biorad Chelex 100.⁽¹⁹⁷⁾ Several standardized Tc-99m-labeled radiopharmaceuticals were prepared satisfactorily. Elution of Sn(II) from the solid phases was found to be less than $0.1 \mu\text{g Sn}$ per preparation.^(196, 197)

Tin metal or a tin alloy has been used as the reductant in the preparation of a thiomalic acid complex of technetium -99. A very dilute Eu(II) salt solution was added, presumably to remove any Sn(II) which had been generated in the reduction reaction.⁽¹⁹⁸⁾

Electrolysis has been used for the reduction of pertechnetate -99m in the presence of suitable ligands. This technique falls into two categories: in the first, tin electrodes do not react directly with the solution, but are used to generate Sn(II) compounds which are in solution during the actual reduction.^(199a,b) In the same vein, a zirconium electrode used in the labeling of albumin with technetium -99m⁽²⁰⁰⁾ was shown to be effective because the protective oxide layer on the zirconium metal was stripped electrolytically, and lower-valent zirconium compounds expelled into the solution were probably responsible for the reduction of the pertechnetate.⁽²⁰¹⁾ In the second category, true electrolysis was used at inert electrodes. Russell reduced pertechnetate -99m at a mercury electrode, taking advantage of the high hydrogen over-voltage of the metal.⁽²⁰²⁾ Steigman, Chin and Solomon used a graphite electrode for the same purpose, and made $^{99\text{m}}\text{Tc}$ -gluconate, pyrophosphate, DTPA and HEDP preparations which yielded satisfactory images in rabbits.⁽²⁰³⁾ In fact, the elimination of the Sn(II) reductant produced a very rapid clearance of Tc-glucoheptonate from the kidneys, suggesting that the tin was responsible for the usual retention of the activity in that organ.

It is possible to perform an electrolytic reduction of pertechnetate -99m without an external applied emf by means of internal electrolysis.⁽²⁰⁴⁾ One can use an H-cell⁽²⁰⁵⁾ in which the cathode is graphite, the anode is zinc metal in either HCl or NaOH solution, the pertechnetate is in the cathode compartment, and the anolyte and catholyte are separated by an agar salt bridge. The electrodes are joined by a copper or other metal wire when electrolysis is to start. The high overvoltage of hydrogen on graphite permits the reduction of pertechnetate in aqueous solutions. The driving force comes from the potential of the zinc ion - zinc system in HCl (-0.763 volts at 25°)⁽²⁰⁶⁾ or in NaOH (-1.216 volts at 25°).⁽²⁰⁷⁾ A number of ^{99m}Tc complexes were prepared in this way, including the DTPA and gluconate complexes, but some air oxidation was found.⁽²⁰⁸⁾

Several oxide bronzes were investigated as solid reductants for pertechnetate -99m. These are non-stoichiometric crystalline phases of transition - metal oxides, usually in ternary systems. They possess high conductivity, approaching that of metals; the tungsten and molybdenum bronzes, which were tried as reductants, are extremely inert, insoluble in water, and resistant to all acids except HF. The transition metal is in two oxidation states, e.g., W(VI) and W(V), and it is not possible to distinguish between them in the lattices, leading to the idea that the "extra" electrons are distributed throughout the lattice.⁽²⁰⁹⁾ It was thought that this "extra" electron might be available for reductions at the surface. It was found that (after a preliminary wash with dilute NaOH), the bronzes (Na_xWO₃ and K₂O.MoO₃) did reduce ^{99m}TcO₄⁻ and a number of complexes were formed, but there was high adsorption of activity on their surfaces (from 20% to 60%).⁽²¹⁰⁾

Another type of potential solid reductant is a tin pyrochlore. These are insoluble ternary compounds whose structures resemble that of the naturally occurring mineral pyrochlorite. The Sn(II) compounds which were prepared were Sn₂Nb₂O₇ and Sn₂Ta₂O₇.⁽²¹¹⁾ These reduced pertechnetate - 99m, and various complexes were successfully prepared, but serious adsorption of activity on the solid reductant was observed in all cases.⁽²¹⁰⁾

Tin metal, in the form of 20-mesh ACS grade tin powder (Alpha) was investigated as a solid reductant⁽¹⁹⁸⁾ and was found to be quite satisfactory with little adsorption of activity. Various complexes - gluconate, DTPA, MDP, and others - were chromatographically satisfactory (Sephadex gel chromatography). Incubation for 15-30 minutes of 100 mg of tin metal with 2 x 10⁻³ M TcO₄⁻ (with some tracer ^{99m}TcO₄⁻) with N₂ stirring was effective.⁽²¹⁰⁾

Analyses of several supernatants of 100 mg of a Sn-Ta pyrochlore and of tin metal used in preparing DTPA complexes were carried out by atomic absorption. The pyrochlore yielded 1.0 µg/ml of tin, and the tin metal put 4.1 ng/ml into solution.⁽²¹⁰⁾

M. Tertiary Organic Phosphines and Arsines

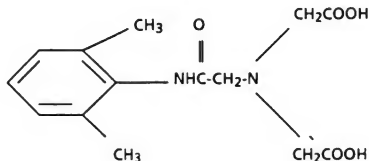
These compounds, like triphenyl phosphine or mixed aryl-alkyl tertiary phosphines and arsines, have served as both ligands and reducing agents. A relatively simple reduction scheme involves the reaction of pertechnetate with a tertiary phosphine. The phosphine-oxide R₃PO is formed, and a phosphine complex - often a Tc(III) complex - is the main product. Risley and VanEtten showed that in the oxidation of triphenylphosphine by potassium persulfate the oxygen of the phosphine oxide came directly from the persulfate, and did not appear to involve the water.^(211a) Tertiary phosphines hence are capable of taking on an oxide ion directly from an oxidant. They are known to take on halogen atoms as well, although the mechanism has not been reported, except for free halogens,^(211b) which form unstable dihalides of the general formula R₃PCl₂. However, the reduction of Tc(IV) hexahalo complexes by phosphines and arsines to form Tc(III) complexes, (because phosphines are 2-electron reductants) suggests that individual halogen atoms are probably transferred to one phosphine molecule before or during the attachment of another to the technetium.

N. Nature of the Reduced Technetium Complexes

There is an unspoken assumption in the search for reducing agents which can replace SnCl_2 . It is that in the presence of a particular ligand, the same technetium complex will be formed regardless of the reductant. While this may be true in general, several exceptions to this assumption have appeared.

In an attempt to reduce quadrivalent technetium $(\text{NH}_4)_2\text{TcCl}_6$ to a lower oxidation state, it was found that hydroxylamine hydrochloride and ammonium chloride yielded a pink crystalline material in which the technetium was believed to be in the +2 state, and in which it was thought that the composition was $[\text{Tc}(\text{NH}_2\text{OH})_2(\text{NH}_3)_3]\text{Cl}_2$ - that is, a hydroxylamine complex.²¹³ It was thought that the hydroxylamine served as both a ligand and a reducing agent. However, Armstrong and Taube found subsequently that the pink compound was a Tc-nitrosyl complex; trans- $[\text{Tc}(\text{NH}_3)_4(\text{H}_2\text{O})\text{NO}]\text{Cl}_2$.²¹³ In this system a breakdown product of the reductant took part in the complexation reaction. This has been observed before; the reaction is called reductive nitrosylation.²¹⁴ Recently, it has been used to prepare the Re(I) complex anion $[\text{Re}(\text{NO})(\text{NCS})_3(\text{H}_2\text{O})]^{1-}$ from perrhenate, thiocyanate and hydroxylamine.²¹⁵

Baldas and Pojer found that the reduction of pertechnetate -99m by formamidine sulfinic acid yielded unexpected results. A complex was formed in the absence of any added ligand, and showed non-specific organ distribution in animals.²¹⁶ When the reduction was performed in the presence of diethyldithiocarbamate as ligand, a non-polar complex was obtained which was concentrated in the livers and intestines of mice.²¹⁷ When they prepared a Tc-99m labeled HIDA (Tc-N-[2,6-dimethylcarbamoylmethyl]iminodiacetic acid) with formamidine sulfinic acid, the resulting complex or complexes showed different chromatographic and biological behavior from that of the conventional



(2,6-dimethylcarbamoylmethyl)imino diacetic acid

SnCl_2 -HIDA preparation.²¹⁸ These studies led to work with $^{99}\text{TcO}_4^-$ and the isolation of a number of technetium complexes. The reduction of pertechnetate -99 in the presence of formamidine sulfinic acid and sodium diethyldithiocarbamate yielded a Tc(III) dithiocarbamate complex²²⁰ with a $\text{Tc}=\text{O}$ bond, and reduction with hydrazine yielded a Tc(V) dithiocarbamate complex²²¹ with a $\text{Tc}\equiv\text{N}$ triple bond.^{219, 220} Still another hitherto unknown complex of technetium was formed in which part of the complex came from the reducing agent sodium azide (NaN_3). When ammonium pertechnetate was

treated with the azide in concentrated HCl or concentrated HBr, an air-stable Tc(VI) complex was formed; e.g., $[\text{Tc}(\text{NCl}_4)_4]^{1-}$, isolated as the tetra-*n*-butylammonium or tetraphenylarsonium salt.¹²²³

A less well-defined but nevertheless definite example of different products arising from the use of different reducing agents of pertechnetate-99m was found in the labeling of human serum albumin. An early method of labeling albumin with $^{99\text{m}}\text{Tc}$ was based on the reaction of pertechnetate with ascorbic acid containing ferric chloride in neutral solution, adding albumin, adjusting the pH to 2, and then raising it to pH 5-6.¹⁷³¹ In this procedure, it was later established that blocking the one free sulfhydryl group on the albumin very markedly reduced the yield of Tc-labeled albumin. Two blocking agents were used: N-ethylmaleimide, and (very dilute) mercuric chloride.¹²²³ On the other hand, when SnCl_2 was used as the reducing agent,⁷²⁴ or FeSO_4 ,¹²²⁵ prior blocking of the sulfhydryl group with N-ethylmaleimide did not decrease the efficiency of Tc-binding noticeably. However, the addition of ascorbic acid to the FeSO_4 albumin mixture did markedly decrease the yield of labeled albumin when the protein was first treated with N-ethylmaleimide or HgCl_2 .²²³ It should be noted that the solutions in the latter research were purged with nitrogen. It can be concluded that there is more than one binding site for reduced pertechnetate on HSA, and that the reducing agent which is used can make a difference in determining the site of binding.

These examples show that more attention must be paid to the products of reaction of pertechnetate with reducing agents, and that more study of the mechanisms is also required.

VI.

Tchnetium (VI) Compounds

A. Tc(VI) Oxygen Compounds

Gerlit reported that hydrazine in cold alkali reduced pertechnetate to a Tc(VI) compound which disproportionated to Tc(VII) and Tc(IV) on dilution.²²⁶ⁱ



The work was repeated by Rulfs, Pacer and Hirsch.²²⁷ⁱ They failed to isolate a Tc(VI) compound from the hydrazine treatment. A reddish-brown solution appeared from which they obtained an impure pink-gray solid, probably contaminated with the sought-for $\text{Ba(TcO}_4)_2$. There was some TcO_2 which they attributed to disproportionation.

Astheimer and Schwochau reduced pertechnetate coulometrically in acetonitrile to Tc(VI). The half-wave potential was -1.74 volts versus saturated calomel, compared to -2.30 volts for perrhenate, showing that pertechnetate is more easily reduced.²²⁸ⁱ They prepared the violet tetramethylammonium salt, $((\text{CH}_3)_4\text{N})_2 \text{ TcO}_4$, and the violet-blue K_2TcO_4 , and found that in water the salts disproportionated to form Tc(V), not Tc(IV):



Astheimer et al also reported that the diffuse reflectance spectrum of the blue crystals showed a band near 400 nm, and that the effective magnetic moment was 1.60 BM, which was reasonable for a Tc(VI) compound.²²⁹ⁱ

The existence of the Tc(VI) anion in water was confirmed by polarography on mercury of pertechnetate in 1 M NaOH.²³⁰ⁱ In the presence of gelatin there is a 1-electron reduction to TcO_4^{1-} followed by disproportionation:



In the absence of gelatin, reduction to Tc(V) proceeds directly.

In pulsed electron irradiation studies of neutral^{230i, 231i} and alkaline²³¹ⁱ pertechnetate, the technetate anion was produced as a transient species. The earlier study in alkali²³¹ⁱ detected technetate polarographically by means of rapid-scan cyclic voltammetry (100 volts/second). The reverse scan showed that the $\text{TcO}_4^{1-} - \text{ TcO}_4^{2-}$ couple in alkali was almost reversible, at -0.61 volts versus the normal hydrogen electrode. One study in the neutral solution²³¹ⁱ was made by measuring optical absorption spectra following the pulsed irradiation, and showed an apparent peak at 320 nm,

together with the hydrated electron peak at 780 nm. In contrast to the earlier study in alkali,⁽¹⁵¹⁾ no peak in the 500-600 nm region was reported. A later study in both alkaline (pH 13) and in unbuffered aqueous solution showed the technetate decay rate to be dependent on pH, and reported an absorption band at 320 nm.⁽²³¹⁾

$$k = 1.5 \times 10^5 \text{ M}^{-1} \text{ s}^{-1} \text{ }^{(230)}$$

$$k = 1.5 \times 10^7 \text{ M}^{-1} \text{ s}^{-1} \text{ }^{(230)}$$

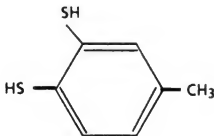
$$k = 1.3 \times 10^8 \text{ M}^{-1} \text{ s}^{-1} \text{ }^{(231)}; \text{ more stable at pH} > 10.$$

A pulsed radiolysis study of perrhenate showed a 2nd order of kinetic dependence on concentration. The disproportionation constant was $1.7 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$. Tc(VI) compounds were prepared in solution by Kirmse and Stach.⁽²⁴⁷⁾ They added 1 mg of KTcO_4 to 1 ml of concentrated H_2SO_4 , and then added concentrated HCl in drops. They obtained a deep blue solution with an absorption maximum at 572 nm, like that reported by earlier workers.⁽²⁴⁸⁾ The EPR spectrum, whose characteristics were recorded, was consistent with that of an oxo-Tc d¹ system. The compound in solution was unstable, and underwent serious decomposition within several hours.

It was found that nitrido technetium(V) compounds could be oxidized to Tc(VI) by chlorine in chloroform.⁽²⁴⁹⁾ The EPR spectra were again consistent with those expected of d¹ complexes. Solutions showed much weaker EPR signals within several hours.

B. Tc(VI) Sulfur Compounds

Until a few years ago, tris-dithiolates were the only known stable set of complexes which are based on Tc(VI). In the synthesis of this or the corresponding rhenium compound, if one starts with a (V) or a (VII) compound, the first member of this series which is formed is an uncharged (VI) complex. The complexes in question are transition-metal complexes which contain ligands with two sulphydryl groups on adjacent carbons, and allied with an unsaturated center, as in toluene-3,4-dithiol.



toluene-3,4 dithiol (tdt)

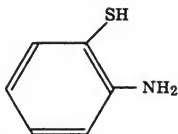
These were the first compounds with a coordination number 6 which are not octahedral. They are trigonal-prismatic. In addition, they undergo facile oxidation and reduction reactions with no change in their donor set.

There is some uncertainty about the actual oxidation state of the metal ion. Thus, for the rhenium complex of toluene-3,4-dithiol which was the first trigonal-prismatic 6-coordinate transition-metal complex to be crystallographically characterized,⁽²³⁴⁾ it was possible to draw two limiting cases:

to assign the VI state to the rhenium, counting the sulfhydryde charge as -1, or else to treat the compound as a Re(O) complex with mercaptide radicals, as a consequence of charge delocalization. In other words, in these two limiting cases, the rhenium retains all its valence electrons or loses all. Such unsaturated ligands were termed non-innocent ligands by Jorgensen.⁽²³⁵⁾ McLeverly, in reviewing transition-metal complexes of this type, wrote that it was inappropriate to use formal oxidation states for them.⁽²³⁵⁾ In unsaturated ligands, the highest filled and/or lowest empty orbitals are near the energy of the metal d levels. In the case of the rhenium complex, the magnetic moment is 1.79 BM, corresponding to one unpaired electron, consistent with a Re(VI) state. However, esr measurements showed that the electrons are predominantly on the ligands, so that an intermediate oxidation state is present.⁽²³⁶⁾ There is an additional reason to argue that the rhenium is in some high oxidation state. Gardner et al, following earlier work with Ni(II) compounds containing amino groups, prepared rhenium tris-o-aminobenzene thiol complexes. In these compounds, the amino groups were deprotonated, forming amido (NH^{1-}) ions.⁽²³⁷⁾ Usually high-valent metal ions like Re(V) or Re(VII) form heavily oxygenated anions like ReO_4^- or else cations like ReO_2^+ , in order to minimize the high central positive charge. In the tris-o-amino-benzenethiol complexes, which contain no oxo atoms, the high positive charge on the central Re atom makes the protons on the amino groups highly acidic. These rhenium compounds undergo facile reversible oxidation-reduction reactions in acetonitrile with 1-electron transfers. The rhenium (VI) tris-dithiolate was oxidized to the +7 state ($E_{1/2} = -0.065$ volts) or reduced to the +4 state (-1.577 volts) and the +3 state (-2.375 volts). Technetium forms a similar set of compounds, although when they were first made, their nature was not recognized. In 1961, Miller and Thomason developed a method of analysis for pertechnetate-99 which was based on its reaction with toluene-3,4-dithiol.⁽²³⁸⁾ They found it necessary to control the experimental conditions very carefully. Different solvents produced different absorption spectra with (presumably) the same complex.

Kawashima and his co-workers prepared the neutral $\text{Tc}(\text{tdt})_3$ complex from KTcO_4 and zinc dithiolate in acid solution. It was possible to study the oxidation of the neutral $\text{Tc}(\text{tdt})_3$ complex to the Tc(VII) state in dichloromethane, and to reduce the (VI) compound to the (V) and (IV) states (at least polarographically).⁽²³⁹⁾ The reduced species could also be made by the addition of ligands like triphenylphosphine, pyridine or o-phenanthroline. However, unlike other metal tris-dithiolates, the technetium compound appeared to polymerize when the Tc(VI) compound was further reduced. The authors explained the so-called solvent effect reported by Miller and Thomason in terms of oxidation-reduction reactions between the complex and dissolved water or polar solvent. Johannsen and Spies investigated the formation of the tris-o-aminobenzenethiol (abt) complex of technetium.⁽²⁴⁰⁾ The compound was formed either by the reduction of pertechnetate by excess ligand (the S-H group functioning as the reductant) or by a substitution reaction with a labile Tc(V) complex. On standing in air, the brown Tc(V) compound changed into a green compound, identified as the neutral $\text{Tc(VI)}(\text{abt})_3$ complex. It was easily reduced by SnCl_2 or by excess o-aminobenzenethiol to the brown Tc(V) complex. Solid quaternary ammonium or arsonium salts of the Tc(V) (i.e. $\text{Tc}(\text{abt})_3^-$) anion were prepared. The Tc(VI) compound in solution was characterized by esr measurements, which were very close to those reported by Stiefel et al for the corresponding Re(VI) compound.⁽²⁴¹⁾

Baldas and his co-workers prepared the $\text{Tc(VI)}(\text{abt})_3$ neutral complex from NH_4TcO_4 and o-aminobenzenethiol in HCl solution, and isolated crystals whose structure was determined by X-ray

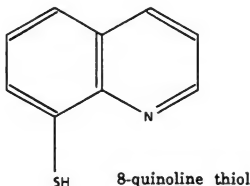


o-aminobenzenethiol(abt)

diffraction.⁽²⁴²⁾ The average $\text{Tc} = \text{N}$ distance was $1.995 \text{ \AA}$, greater than the distance in $(\text{S}_2\text{CNET}_2)_2\text{Tc.N}$ but less than that in $\text{TcO}_2(\text{cyclam})^{+}$. From the structural point of view, this is the first demonstration of a trigonal-prismatic Tc(VI) complex. From esr studies of solutions of both the Tc(VI) and Re(VI) compounds, it was concluded that both tended to form aggregates in solution.⁽²⁴³⁾

C. Tc(VI) Nitrido Compounds

A different type of Tc(VI) complex was discovered by Baldas and his collaborators; it is described briefly in an earlier section. If NH_4TcO_4 and NaN_3 are reacted together in concentrated HCl or HBr , a tetra-halo-nitrido-technetate(VI) anion is formed, which can be crystallized as the tetraphenylarsonium salt.⁽²²²⁾ This compound is isostructural with the corresponding quaternary arsonium salts of Re , Os , Mn , and Ru . The $\text{Tc} = \text{N}$ distance is $1.581 \text{ \AA}$, the $\text{Tc}-\text{Cl}$ distance is 2.322 or $1.905 \text{ \AA}$, and the anion has C_{4v} symmetry. An esr measurement showed that the compound behaved as if it had a single unpaired electron, very much like CrOCl_4^- and MoOCl_4^- . A number of compounds of radiopharmaceutical interest were prepared by substitution reactions between $^{99}\text{TcNCl}_4^-$ and ligands that included MDP, DTPA and cysteine.^(245a) They were characterized by uv-visible absorption spectra and by HPLC. It was possible to reduce the tetrachloro Tc(VI) compound to Tc(V) -nitrido complexes by means of the reducing ligands P(Ph)_3 , KNCS , $\text{Na}(\text{S}_2\text{CNET}_2)$ and 8-quinolinethiol to yield:



8-quinoline thiol

$\text{TcNCl}_2(\text{P(Ph)}_3)_2$, $(\text{NEt}_4)_2[\text{TcN}(\text{NCS})_4 \cdot (\text{CH}_3\text{CN})]$, $[\text{TcN}(\text{S}_2\text{CNET}_2)_2]$ and $[\text{TcNL}_2]$ (in which L represents the 8-quinolinethiol moiety). The structure of the last complex was determined. It was a distorted square pyramid.⁽²⁴⁶⁾

VII.

Technetium(V) Compounds

Until recently the opinion was widely held that the aqueous chemistry of technetium was largely limited to compounds of Tc(VII) and Tc(IV), and that Tc(V) compounds would be unstable in water because of disproportionation.⁽²⁵⁰⁾ This opinion was held in spite of the existence of a large number of stable octahedral complexes of Re(V) which had multiple bonds between the metal and oxygen or nitrogen atoms.⁽²⁵¹⁾ Chronologically, the first established case of the existence of a Tc(V) compound in water came from a study of Tc(V) citrate.⁽²⁵²⁾ This was soon followed by a study of the Tc(V)-gluconate and -glucoheptonate complexes prepared by SnCl₂ reduction of pertechnetate.⁽²⁵³⁾ These are examples of a large number of actual and potential polyhydroxy compounds that also serve as sources of other Tc(V) complexes by displacement of part or all of the polyhydroxy ligand.⁽²⁵⁴⁾ This and related researches were based on chemical investigations of already established useful radiopharmaceutical products, and were carried out on aqueous solutions of the complexes.

A different approach consists of the production (mostly in non-aqueous solutions and often by substitution reactions of the Tc(V) complexes TcOCl₄⁻ and TcOBr₄⁻) of crystalline solids whose stoichiometries, coordination and structures could be definitively characterized. This is true of the dithiol complexes described below. At the least, it broadens the scope of known Tc(V) chemistry, particularly in relation to the much more extensive published material on rhenium compounds. With some luck, if the chelate is well characterized and stable, the corresponding ^{99m}Tc radiopharmaceutical might have the same unambiguous structure and properties, even in extremely dilute solution. With more luck, it or one of its congeners might have desirable properties *in vivo* for diagnoses. Because numerous Tc(V) complexes emerged from the Tc(V) dithiol studies, the sulfur chemistry of Tc(V) will be discussed before the oxygen and nitrogen chemistry.

A. Sulfhydryl Compounds

1. Synthesis and Structure of Monodentate Sulfur-Based Compounds

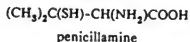
Sulfur, which is less electronegative than oxygen or nitrogen, has very different bonding properties. It has low-lying empty 3d orbitals which are available for electron donation by other atoms, and its coordination number can be as high as 6.⁽²⁵⁵⁾ Compounds with sulfur-sulfur bonds are common, as are polymers if the geometry of the system permits them. With cysteine as a ligand, first row transition metals form a family of complexes, including polymerized species.



Cysteine

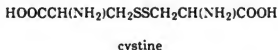
Thus, for zinc(II), there are the following, among others, which have been identified in solution:

$\text{Zn}(\text{HL})_2$ (H_2L is cysteine), $(\text{Zn}_3\text{L}_2(\text{HL}))^{1-}$, $\text{Zn}_3\text{L}_4^{2-}$, $(\text{ZnL}(\text{HL}))^{1-}$ and ZnL_2^{2-} .⁽²⁵⁶⁾ With penicillamine, there are no polymeric species reported, presumably because of the steric hindrance to polymerization offered by the two methyl groups. When polymers form, they often do so by means of a sulfide bridge between metal atoms. Double mercaptide bridges are also known to form, as with Fe(III) and Mo(V) complexes.⁽²⁵⁷⁾



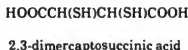
Technetium(V) gluconate, formed by the addition of 1 mole of Sn(II) for each mole of $^{99}\text{TcO}_4^-$ in a gluconate solution, was reported by Steigman and his collaborators to react almost immediately with cysteine in acid aqueous solution. A Job or continuous variations study showed that there was a 1:1 cysteine-technetium complex with λ_{max} at 420 nm and the molar absorptivity coefficient = $2300 \text{ M}^{-1} \text{ cm}^{-1}$, a 2:1 complex absorbing at the same wavelength with coefficient $3700 \text{ M}^{-1} \text{ cm}^{-1}$, and possibly other complexes. The complexes, which appeared to be stable, may have been mixed-ligand complexes. The 2:1 complex was more stable against acid attack than the corresponding 2:1 Ni(II) complex, which would make its overall formation constant (i.e. K_1K_2) at least 10^{20} .⁽²⁵⁴⁾ It was also found by the same investigators that the direct reduction of pertechnetate-99 by cysteine itself produced an unstable species and TcO_2 , but if the reduction was performed in the presence of gluconate a stable yellow species was obtained.

Johannsen and his co-workers investigated the formation of complexes of technetium with cysteine, cystine derivatives, and penicillamine.⁽²⁵⁸⁾ The Tc(V) complexes were formed either by



reduction of pertechnetate by the mercaptan, or by substitution reactions of TcOCl_4^- (in solution) or of Tc(V) citrate (prepared by adding 1 mole of Sn(II) for each mole of $^{99}\text{TcO}_4^-$ in a citrate buffer). The direct reduction of pertechnetate by cysteine first produced a yellow complex followed by a red compound and a green compound. These were separated chromatographically. There was also an unidentified polymer, and some TcO_2 . The separated products appeared to be stable over a period of time. The purified yellow Tc(V) compound (λ_{max} = 420 nm, molar absorptivity = $2300 \text{ M}^{-1} \text{ cm}^{-1}$) is probably the 1:1 Tc-cysteine complex made by displacement from Tc(V)-gluconate.⁽²⁵⁴⁾ The electronic spectra of chromatographically purified products obtained by substitution reactions were the same as those produced by the reduction of pertechnetate-99. In this connection, the reduction of pertechnetate by SnCl_2 was much more rapid than that by cysteine.

A detailed examination was made of the kinetics of the reduction of $^{99}\text{TcO}_4^-$ by mercaptans.^(259, 260) In each case the reaction was first order in mercaptan and pertechnetate concentrations at a fixed acidity. For cysteine and for racemic dimercaptosuccinic acid, the negative logarithm of the



velocity constant was proportional to the H_0 of the acid solution (that is, the Hammett acidity function for uncharged bases). The more appropriate acidity function would have been the H^- -function, describing the reaction of a negatively charged base with a proton, and producing an uncharged conjugate acid. Nevertheless, it is clear that the reaction is strongly acid catalyzed. In this respect, the pertechnetate anion belongs to the group of oxyanions like permanganate and dichromate whose rates of reduction are heavily dependent on acid concentration.⁽²⁶²⁾ It is also known that these rates tend to parallel the rates of exchange of the same oxyanions with H_2^{18}O . For the oxidants

permanganate, pertechnetate and perrhenate, the following equation describes the general pattern of H_2^{18}O exchange rates.^(263, 264)

$$\text{Rate} = K[\text{XO}_4^{1-}][\text{H}^+]^2$$

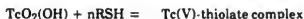
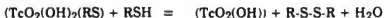
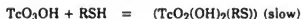
Initially, in the case of the perrhenate-water exchange,⁽²⁶³⁾ it was concluded that the H^+ concentration entered the rate equation to the first power. This was based on a calomel-glass electrode measurement of pH. Entering the actual concentration of added acid rather than the antilog of the measured pH resulted in a much better fit for the square of the acid concentration in the rate equation.⁽²⁶³⁾ The relationship of the rate to the acidity is explained by the following equations:



This is not regarded as a displacement reaction by water, but rather as a preliminary labilization of oxygen by protons, weakening the $\text{X} = \text{O}$ bond in the XO_4^{1-} anion. It is possible that the acid catalysis of the pertechnetate-cysteine reaction may follow a similar catalytic course.

2. Mechanism of Reduction of Pertechnetate by Cysteine

The following mechanism was advanced to explain the kinetics of the reduction of pertechnetate by cysteine:⁽²⁵⁹⁾



It has been hypothesized for some time that the redox reactions of oxyanionic oxidants probably involve prior substitution of the reductant in the coordination sphere of the oxidant.⁽²⁶²⁾ This is particularly true of the reactions of Cr(VI) but is believed to be general. In the present case, the second step - the entry of a mercaptan molecule into the coordination sphere of pertechnetate (but, without an added proton) is logical. The third step - the reaction of a mercaptide - substituted Tc(VII) with a molecule of RSH to yield R-S-S-R and Tc(V) - is, however, not in accord with the known redox chemistry of thiols. The latter are oxidized in one-electron steps, generating thiol free radicals. These one-electron exchange steps have been proposed, for example, to explain the reaction between Cr(VI) and cysteine in acid solution.⁽²⁶⁵⁾ The proposed 2-electron exchange in the third step is not consistent with this pattern of cysteine behavior. What is more likely is a preliminary weakening of a $\text{Tc} = \text{O}$ bond by protons, followed by the entry of a cysteine molecule into the technetium coordination sphere, followed by a slow internal reaction yielding Tc(VI) and a thiyl radical, followed by a more rapid redox reaction of Tc(VI) with a second cysteine molecule to yield Tc(V) , which then coordinates mercaptide groups rapidly. The $\text{VI} \rightarrow \text{V}$ reduction is probably a more rapid reaction than the $\text{VII} \rightarrow \text{VI}$ reaction because it is known that a lower oxidation state for an oxyanion oxidant means a faster exchange rate with H_2^{18}O . Thus, in the series ClO_4^{1-} , ClO_3^{1-} , ClO_2^{1-} , etc., the water exchange rate increases very rapidly even in going from perchlorate to chlorate.⁽²⁶²⁾ As a case in point, when an aqueous perrhenate solution was irradiated with ^{60}Co gamma photons, the exchange rate with H_2^{18}O increased by 100-1,000 fold, compared with unirradiated perrhenate.⁽²⁶⁴⁾ The increase in exchange rate was attributed to the faster exchange of rhenate (ReO_4^{1-}) compared with perrhenate. It was assumed that the rhenate was formed by the reaction between perrhenate and solvated electrons. These

considerations have led us to suggest that the rate-determining step in the reduction of pertechnetate by cysteine may be the formation of Tc(VI).

We have devoted some attention to this work because there are very few studies of the kinetics and mechanisms of reaction of technetium compounds in general and in particular in its radiopharmaceutical chemistry.

3. Crystal Structure Determination

To date the only reported structure analysis of a monothiol Tc(V) complex is that of a d-penicillamine compound, $[\text{TcO}(\text{D-penicillamino})-(\text{D-penicillamine})]$.²⁶⁶ It is a 6-coordinate Tc(V) complex with two 5-membered rings each bearing a sulfur atom and a nitrogen atom bonded to the technetium. The 5th position is occupied by a carboxylate oxygen. The complex was prepared by the substitution reaction between TcOCl_4^- and D-penicillamine in concentrated HCl. A complex with a similar visible absorption spectrum was prepared by Yokoyama and his collaborators from the TcCl_6^{3-} anion and D-penicillamine.²⁶⁷ This raises the question: Was the Tc(V) complex reduced by excess ligand or was the Tc(IV) complex (from TcCl_6^{3-}) oxidized by air? The resolution of this question has not been forthcoming.

B. Synthesis and Structures of Bidentate Sulfur-Based Complexes

1. Introduction

The fairly complete characterization of a number of technetium complexes, including the study of the properties of Tc(V) chelates of bidentate thiol ligands, has broadened perspectives and furnished at least the beginning of a generalized approach to the structural chemistry of Tc(V) complexes (unfortunately, not all studied in water). Two notes appeared simultaneously in 1978. In one, pertechnetate was reported to have reacted with an impurity in thioglycolic acid and was reduced



Thioglycolic Acid

to the oxotechnetium bis (thiomercaptoacetate) anion, which was isolated as the tetra-*n*-butylammonium salt: $n\text{-Bu}_4\text{N}[\text{TcO}(\text{SCH}_2\text{COS})_2]$.²⁶⁸ In the other work, pertechnetate was reduced by NaBH_4 in ethanol in the presence of 1,2- or 1,3-dithiols and the products were isolated as the tetraphenylarsonium salts, e.g., $\text{Ph}_4\text{As}[\text{TcO}(\text{SCH}_2\text{CH}_2\text{S})_2]$.²⁶⁹

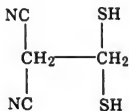
In both reported Tc(V) dithiol complexes, the four sulfur atoms of the 5-membered rings are nearly co-planar. The technetium atom is about 0.8 Å above that plane, and the oxygen atom lies above it. The Tc-O distance is 1.6-1.7 Å. The structures are thus approximately square pyramidal with the oxygen at the apex. The IR and Raman spectra of the 1,2-ethylenedithiol complex show a band at 940 cm^{-1} ; in the case of the other compound, it is at 950 cm^{-1} . These bands are assigned to the Tc=O stretching frequency by comparison with many Re(V) oxo compounds.²⁵¹

The dithiol complexes of Tc(V) should be extremely stable against dissociation. With most transition metal complexes, like amine complexes, the formation constant of the first member of the series is usually greater than that of the second, and so on. That is $K_1 > K_2 > K_3$, etc., if only for statistical reasons.²⁵⁶ Thus for the complex of Cu^{2+} and NH_3 , $\log K_1 = 4.04$, $\log K_2 = 3.43$, $\log K_3 = 2.80$, $\log K_4 = 1.48$. However, sulfur-containing ligands like cysteine and its methyl ester form complexes with transition metals in which the reverse order of stability is found. For nickel-cysteine complexes, $\log K_1 = 9.0$ and $\log K_2 = 11.1$.^{256b} Formation of the first metal-thiol bond facilitates that of the second bond. The explanation which has been offered is that there is some type of delocalized or pi bonding between the sulfur atom and filled orbitals from the metal which supplements the sigma

bonding which had resulted from the donation of lone electron pairs to the metal from the ligand.⁽²⁵⁵⁾ The overall effect, coupled with the additional stabilization which is to be expected from two 5-membered rings should make complexes of bidentate thiols of the appropriate geometry and spacing extremely stable against dissociation.

The displacement reaction of the monothiol cysteine on Tc(V) gluconate⁽²⁵⁴⁾ was extended to dithiols⁽²⁷⁰⁾. (1,1)-dicyanoethane (2,2) dithiol also reacted with Tc(V) gluconate to form a 4-membered ring- a 1, 1 dithiolate complex of technetium.⁽²⁷¹⁾ Its Tc=O IR stretching frequency was at 970 cm^{-1} . Various technetium dithiocarbamates of the general formula $\text{TcO}(\text{S}_2\text{CNR}_2)$ in which the R group represented various alkyl residues were prepared and characterized by spectroscopic methods.⁽²⁷²⁾

The unsaturated thiol ligand 3,4-toluenedithiol, which under other conditions yields the tris-dithiolate complexes of Tc(VI), produces the oxotechnetium(V) bis -(3,4-toluenedithiolate) anion, very much like the bidentate thiol ligand.⁽²⁷³⁾ The reaction was run in aqueous alkali, and the pertechnetate was reduced with sodium dithionite in the presence of the ligand. Structural analysis



1,1 dicyanoethane(2,2)dithiol

on crystals was not performed. The compound was characterized by its IR spectrum, by elemental analysis and by its field desorption mass spectrum. In this connection, similar experiments have been performed on molybdenum⁽²⁷⁴⁾ and rhenium⁽²⁷⁵⁾ compounds, which can also form either bis (normal) or tris complexes with unsaturated 1,2-dithiolates or p-aminobenzenethiols. Kinetic measurements at 25°C were made of the displacement reaction between Tc(V)-gluconate and meso-2,3-dimercaptosuccinic acid as well as its dimethyl ester.⁽²⁷⁶⁾



gluconic acid

The increase in absorbance at 400 nm was measured as a function of time. The reaction appeared to be first order in the technetium and dithiol concentrations. The general reproducibility was poor. The effect of acidity on the reaction rates was: first order in hydrogen-ion concentration for the ester, and roughly half-order for the acid. The hypothesis in the case of the ester was that the hydronium ion split the Tc-carboxylate bond of the gluconate complex in a reversible equilibrium, and that the product of this reaction slowly reacted with one dithiol molecule. A second dithiol then rapidly displaced the still-coordinated gluconate ligand. However, since the carboxyl group of the gluconate does not seem to be involved in binding technetium(V),⁽²⁷⁷⁾ this mechanism does not appear to be relevant.

A large number of bis (dithiolato)Tc(V) complexes have been synthesized and characterized in several laboratories.^(278, 271, 279) They have reinforced the conclusions which have already been reached about the general stability and structural characteristics of this class of compounds.

2. Mixed Sulfur-Oxygen and Sulfur-Nitrogen Compounds

The structure of tetraphenylarsonium bis (2-mercapto-ethanolato) oxotechnetate, $(\text{Ph}_4\text{As})[\text{TcO}(\text{SCH}_2\text{CH}_2\text{O})_2]$ is an almost square-based pyramid very much like those found in the dithiol complexes.⁽²⁸⁰⁾ There is some distortion in the 5-membered rings because of the difference in Tc-O and Tc-S bond lengths. The distortion causes the formation of a trapezoid in the plane. The Tc=O distance is 1.72 Å, a little less than those found in the dithiol complexes. The IR spectrum shows a strong band at 948 cm^{-1} , assigned to the Tc=O stretch.

It can be concluded that the substitution of one oxygen for one sulfur atom in dithiol ligands produces only a small structural change. However, there is a loss of stability. This complex will react in solution with two equivalents of 1,2-ethanedithiol to form $[\text{TcO}(\text{SCH}_2\text{CH}_2\text{S})_2]^-$. It appears to do so by way of an intermediate species which may be a dimer: $[(\text{TcO})_2(\text{SCH}_2\text{CH}_2\text{S})_3]$.⁽²⁶¹⁾

When dissimilar chelating atoms are present in a ligand, it can be expected that cis and trans isomers of the complex will form, and this may present a problem in the preparation of a pure compound. The solid compound which was actually isolated in the cited work⁽²⁶⁰⁾ was the cis isomer. The trans isomer was not physically separated, but was detected in the NMR spectrum of the initial reaction mixture. Cis and trans isomers were also found in the formation of the unsymmetrical mercapthioacetate complex.⁽²⁶⁶⁾

A series of bisimidobisthiolate complexes of Tc(V) were prepared in which the core was TcON_2S_2 .⁽²⁶²⁾ The ligands were dimercaptodiamides in which the sulfhydryl groups were protected by benzoyl groups: $(\text{PhCOS}(\text{CH}_2)_n\text{CONH})_2\text{X}$ ($n = 1$, $\text{X} = (\text{CH}_2)_2$, $(\text{CH}_2)_3$ or $\text{o-C}_6\text{H}_4$; for $n = 2$, $\text{X} = (\text{CH}_2)_2$ and $(\text{CH}_2)_3$ were prepared). Pertechinate-99 was reduced by sodium dithionite in alkaline solution in the presence of the ligands to yield complexes of the type $[\text{TcO}(\text{S}(\text{CH}_2)_n\text{CONXCO}(\text{CH}_2)_n\text{S})]^-$ in which $n = 1$, $\text{X} = (\text{CH}_2)_2$, $(\text{CH}_2)_3$ or $\text{o-C}_6\text{H}_4$; for $n = 2$, $\text{X} = (\text{CH}_2)_2$. The amide groups were deprotonated in the formation of the complexes. The technetium was 5-coordinate in these compounds; the structural characteristics resembled those of the mercaptoethanol Tc(V) compounds. Thus, in the simplest of these, based on ethylene bis (2-mercaptoacetamide),⁽²⁶³⁾ the basal plane was a distorted square pyramid with some ring angle distortion, the Tc=O distance was 1.679 Å and the technetium atom was 0.771 Å above the plane.

Another type of mixed S-N compound of technetium is found in the diaminodithiol (DADT) compounds. When technetium is coordinated to these ligands, the resulting complexes are neutral, quite stable, and exhibit a lipophilicity which depends on the overall structure of the ligand.⁽²⁸¹⁾ While a large part of the work was performed with Tc-99m,^(283a) a particular ligand-(N-piperidinyethyl) hexamethyl diaminodithiol-was reacted with $^{99}\text{TcO}_4^-$, reduced in basic solution by sodium hydrosulfite, and compared (by HPLC and paper chromatography) with the $^{99\text{m}}\text{Tc}$ complex. It turned out that there were two complexes in each system. Characterization of the ^{99}Tc complexes suggested that the two ^{99}Tc (NEP-DADT) complexes were syn and anti isomers in which the N-piperidinyethyl side chain was located either syn or anti to the Tc=O core. In the synthesis of the complexes, one of the two secondary amine groups lost a proton, whereas the other did not. When this was coupled to the loss of two protons from the two sulfhydryl groups, the net charge on the complex was reduced to zero.^(283c)

A number of diaminodithiol ligands with pendant side-groups- NH_2 , OH, COOH, or phenyl OH-were prepared and coupled with Tc-99m by reducing pertechinate with SnCl_2 or NaBH_4 .^(283d) While there has been no characterization of these complexes, it is probable that the side-chain groups are not directly involved in coordinating the technetium. If so, this points to high stability for the $\text{N}_2\text{S}_2\text{-Tc}$ linkage.

3. Conclusion

In summary Tc(V) forms complexes with various dithiols in which the coordination number of the metal is 5 in crystals, and in which there is no group trans to the Tc = O bond. With dithiols, Tc(V) can form 4-, 5- and 6-membered rings. If a nitrogen atom is substituted for one of the sulfur atoms, as in N,N-ethylene bis (2-mercaptoacetamide), only a 5-membered ring has been found. The attempts to form a six-membered ring by the inclusion of an additional CH₂ group were unsuccessful.²⁸⁴ⁱ The short Tc = O distance is characterized by an IR stretching frequency in the 900-1,000 cm⁻¹ region. This band offers a convenient means of identifying the Tc = O moiety in Tc(V) compounds. This group appears to impart a degree of inertness to the complex, the magnitude of which will depend on the nature of the coordinating ligands. This inertness arises from spin pairing in the d² configuration which is promoted by the introduction of sulfur atoms into the metal coordination sphere. The two d electrons behave like a closed shell when they are paired.²⁸⁵ This does not mean, however, that all Tc(V) compounds are diamagnetic. There is a temperature-independent paramagnetism (TIP) reported for the compounds which have been discussed which is induced by an applied magnetic field, and whose magnitude depends on that of the field.²⁸⁶ⁱ

There is also a trans effect associated with M = O bonds (where M represents a metal) which has already been noted in Re(V) compounds.²⁵¹ⁱ Groups which are trans to the oxide ion (in a hypothetical or actual 6-coordinate compound) are rendered labile, in both a kinetic and an equilibrium sense. In the solid state the complexes discussed thus far are 5-coordinate. In solution, it is possible that there is weak solvation in the position trans to the Tc = O bond. Only a qualitative statement can be made about the trans effect in octahedral substitution. More quantitative knowledge in this area has come from the study of square planar complexes.²⁸⁷ⁱ The magnitude of the trans effect depends on the nature of the ligands.

C. Tc(V) Complexes with Oxygen Compounds

1. Introduction

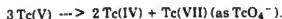
The first demonstration of the existence of a Tc(V)-oxygen-linked complex in aqueous solution was reported by Steigman, Meinken and Richards in a study of the reaction of pertechnetate-99 with excess SnCl₂ in a citrate buffer at pH 7.²⁵⁵ⁱ Polarographic analysis of unreacted Sn(II) showed that there was a rapid reduction of Tc(VII) to Tc(V). No other characterization of the complex or complexes was made. The oxidation state of the technetium was confirmed by Muenze, who found in addition that the absorption spectrum of the Sn(II) reduced Tc(V) complex was the same as that of the product of reaction of the [TcOCl₅]²⁻ anion with citrate.²⁸⁸ⁱ There was a peak near 290 nm whose molar absorptivity coefficient was 3400 M⁻¹cm⁻¹, and a second weak band near 700nm whose coefficient was 30M⁻¹cm⁻¹. Since the reduction by SnCl₂ appeared to produce the same product as the substitution reaction with TcOCl₅²⁻, it can be concluded that there is no Sn(II)-Tc(V) or Sn(IV)-Tc(V) mixed complex. Muenze claimed that the stoichiometry of the complex was 2:1(citrate: Tc), based on a spectrophotometric study of the reduction process. A later spectrometric study of the reaction of n-Bu₄N⁺TcOCl₄⁻ in methanol with citric acid showed that the mole ratio of citrate to technetium(V) was 1.5:1²⁸⁹ⁱ, implying that the complex formed here was at least a dimer of technetium. Since the known citrate complexes of transition metals show extensive changes in charge and in their degree of polymerization with acidity,^{289, 290, 291, 292i} it must be concluded that there is insufficient characterization of the Tc(V) citrate complex or complexes at present.

The first reported study of a gluconate complex of technetium maintained that the reduction of pertechnetate by SnCl₂ in the presence of a gluconate salt produced a Tc(IV)-gluconate complex.²⁹³ⁱ The oxidation state of the technetium was determined by an iodometric titration of the solution, with the implicit assumption that the iodine reacted only with excess Sn(II). Both the analytical method and the chemical conclusions were questioned because of the possibility of oxidation of some reduced form of the technetium by the iodine reagent.²⁹⁴ⁱ Another study of the reduction of pertechnetate by

SnCl_2 in the presence of various polyhydroxy compounds including sodium gluconate and sodium glucoheptonate concluded that there was a large family of Tc(V) compounds formed in dilute alkali.²⁵³ The oxidation state of the technetium in these complexes was established as Tc(V) by the polarographic analysis of excess (unreacted) Sn(II) , by spectrophotometric titrations,²⁵³ and by coulometry at fixed potential.²⁷⁷ The gluconate-technetium ratio was critical in determining the electron number n (the number of electrons taken up by the pertechnetate). In alkaline solution the value of n was 2.0 down to ratio 17. At pH 5, n was almost 2.4 when the ratio was 110. In an iodometric titration performed in air, n was 2.8. The nature of the products formed in the presence of insufficient gluconate was not investigated.

2. Polyhydric Alcohols

In the polyhydric alcohol series starting with ethylene glycol and finishing with perseitol, $\text{C}_7\text{H}_9(\text{OH})_7$, pale pink-violet solutions were formed in their presence when pertechnetate-99 was reacted with excess SnCl_2 at pH 12. The visible absorption bands were near 500 nm, and the molecular absorptivity coefficients were about $100 \text{ M}^{-1} \text{ cm}^{-1}$. A colored complex was formed with 1, 2-propanediol, but TcO_2 was precipitated when 1, 3-propanediol was the ligand. It was concluded that Tc(V) could form alkoxide-based chelates with 5-membered rings, but not with 6-membered rings. The early members of the series - complexes of Tc(V) with ethylene glycol and glycerol - disproportionated rapidly when their alkaline solutions were acidified. Quantitative analysis showed that the reaction was

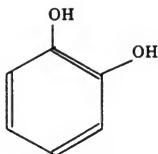


Complexes formed with longer-chain polyols like mannitol showed virtually no change in spectrum on acidification.

These complexes, like those of the polyhydroxy acids described below, are not very stable in water, and require a fairly large excess of ligand for stabilization. This makes it difficult to determine their composition by mole ratio or continuous variation methods. If the ratio of ligand to technetium is too low, the complex decomposes. However, this is not the case in organic solvents like methylcellosolve (ethyleneglycol monomethyl ether). In this solvent, a 1:1 mixture of pertechnetate and SnCl_2 in alkali reacts to form a deep pink-violet compound which does not disproportionate, and is unchanging in time. The prior addition of a polyhydric ligand lowers the solution absorbance at about 510 nm, and one can plot absorbance against mole ratio of ligand to technetium. On this basis, (assuming that the original compound is a solvated Tc(V) compound) it was found that ethylene glycol forms a 1:2 technetium-glycol complex, and that the mannitol complex has a 1:1 stoichiometry.²⁷⁷

DePamphilis et al isolated the Tc(V) ethylene glycol complex as a solid salt. It had the composition $\text{Na}[\text{Tc}(\text{O})(\text{gly})_2]$, in which gly represents the divalent anion of ethylene glycol.²⁸¹

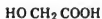
A 1:2 Tc(V) complex of catechol (1,2-dihydroxybenzene) has been prepared as the tetra-n-butylammonium salt.²⁸¹ The $\text{Tc} = \text{O}$ group is at the apex of a pyramidal structure very much like that observed in the Tc(V)-dithiolate complexes.²⁹³ Analysis confirmed an earlier stoichiometric finding in solution.²⁹⁶



Catechol

3. Polyhydric Acids

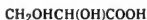
A series of hydroxy-acids was tested as ligands for technetium. When TcO_4^- was reduced by SnCl_2 in an alkaline solution of glycolic or lactic acid, a brown dispersion was formed, which was assumed to be TcO_2 . Longer-chain polyhydroxy acids from glyceric to glucoheptonic formed pink-



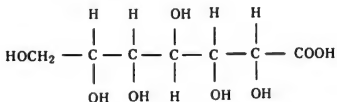
Glycolic Acid



Lactic Acid



Glyceric Acid



Glucoheptonic Acid

violet complexes in alkali with molecular absorptivity coefficients of about 100, very much like the polyol complexes. The glyceric acid complex was stable in alkali and disproportionated rapidly in acid, like the ethylene glycol complex. The gluconate complex showed a single band at 502 nm in alkali. In acid solution two bands appeared at 600 nm and 490 nm. The original 502 nm band reappeared in alkaline solution. The Tc(V) glucoheptonate complex showed similar behavior. This is in marked contrast to the mannitol complex which showed no change in absorption spectrum from pH 12 to pH 3. The similarity in spectra between the polyol and polyhydric acid complexes, the failure to form one of these complexes with a simple alpha-hydroxy acid and the spectral change on acidification of the gluconate and glucoheptonate complexes strongly suggest that the carboxylic acid group is not involved in the binding of technetium to the ligands. The spectral changes on acidification represent either the neutralization of a free carboxylate or the formation of a lactone from the free carboxylate. This conclusion was reinforced by paper electrophoresis experiments with $^{99\text{m}}\text{Tc}$. These showed (relative to $^{99\text{m}}\text{TcO}_4^-$) that the glucoheptonate complex migrated almost twice as fast as the mannitol complex from pH 11 to pH 5. However, at pH 4 and at pH 3 the mobilities were almost the same. At the same time, the mobility of the mannitol complex (relative to $^{99\text{m}}\text{TcO}_4^-$) was essentially unchanged

from pH 11 to pH 3. The conclusion was drawn that the glucoheptonate complex in alkali was more highly charged than the mannitol complex, but that the two had the same charge in acid, and that this was due to the protonation of the free carboxylate group.⁽¹⁷⁷⁾

The mole ratio of glucoheptonate to technetium was found to be 1:1 in 25 molar choline chloride in which the SnCl_2 and pertechnetate-99 concentrations were equal, and to which various aliquots of sodium glucoheptonate solution were added.⁽²⁷⁷⁾ The chemistry of concentrated aqueous quaternary ammonium salt solutions and their role in stabilizing anionic metal complexes has been explained elsewhere.⁽¹⁸⁴⁾

4. Tc-Glucoheptonate

A recently published research established that technetium-99 in the glucoheptonate complex was in the V state.⁽²⁸⁷⁾ There were, however, a number of other properties ascribed to this complex which must be reexamined. In the reported study, the conclusion was drawn that there were two ligand molecules to each technetium atom. This was based on a spectrophotometric mole-ratio plot of the absorbance at 502 nm versus the ratio of glucoheptonate to technetium in a solution which initially contained 0.115 M $^{99}\text{TcO}_4^-$ and 0.115 M SnCl_2 . The pH, which was not adjusted, ranged from about 2 at very low glucoheptonate concentration to 5.6 with a large excess. It was claimed that the spectra were unaltered over the pH range, but that the peak at 502 nm decreased as the pH was lowered. It has already been shown elsewhere that the band shape is changed drastically below pH 5.⁽²⁷⁷⁾ In any event, there are two breaks in the mole-ratio curve: at ratio 2, and near ratio 6.5. The latter is attributed to a "pH effect." The break at ratio 2 is offered as the proof that the composition of the complex is 2 ligands to 1 technetium. The plot shows a smaller slope in the 0-2 mole-ratio interval than after it. It is the difference in slopes which causes the apparent discontinuity in the curve. Otherwise, the overall curve resembles that of a weak complex which requires a fairly large excess of ligand for stabilization. At the 2:1 ratio the absorbance is about 0.08 and the pH is 4. The apparent yield of glucoheptonate complex is less than 15%. The lowered slope in this region may well represent the formation of tin complexes of glucoheptonate;⁽²⁸⁸⁾ the tin may then be in competition with technetium for the ligand. As the glucoheptonate-technetium ratio increases, this competition will become less important.

In the reported study,⁽²⁹⁷⁾ the IR spectrum of a non-crystalline solid sample of the glucoheptonate complex showed a band at 1740 cm^{-1} , which was identified as that of a Tc-carboxylate stretching frequency (Tc-OOCR). However, this is not the carboxylate frequency of a metal-carboxylate complex. Ionized and coordinated carboxylate frequencies are found between 1540 and 1650 cm^{-1} , not far from the uncomplexed carboxylate stretching frequencies in the 1630 - 1575 cm^{-1} interval.⁽²⁹⁹⁾ The band at 1740 cm^{-1} is that of a carbonyl stretching frequency - either a free carboxylic acid group or a lactone.⁽³⁰⁰⁾ The IR spectrum of the solid sample also showed bands at 930 , 970 , and possibly at 785 cm^{-1} . These were assigned to a Tc=O stretch. However, the presence of two bands in the 900 - $1,000\text{ cm}^{-1}$ region raises some question about the homogeneity of the sample. In addition, the band at 785 cm^{-1} introduces a different possibility. Davison and Jones reported that the following IR bands appeared in various Tc(V) cyanide complexes: 910 or 932 cm^{-1} (for the Tc=O stretch) and 785 cm^{-1} for a trans-dioxo ($\text{O}=\text{Tc}=\text{O}$) stretch.⁽¹⁰⁶⁾ Earlier work on various Re(V) complexes showed similar values with similar assignments. The terminal Re=O stretch in mono-oxo and in binuclear (linear) u-oxo compounds is from 912 - 995 cm^{-1} . The trans-dioxo asymmetric stretch is found in the 775 - 835 cm^{-1} interval. The μ -oxo asymmetric stretch in Re-O-Re compounds lies between 720 and 860 cm^{-1} .⁽³⁰¹⁾ The band at 785 cm^{-1} in the IR spectrum of the solid Tc-glucoheptonate may belong to a trans-dioxo compound or to a dimeric Tc-O-Tc complex.

The proton NMR spectra of sodium glucoheptonate and of technetium(V) glucoheptonate solutions in D_2O were measured, and the results were interpreted in terms of the structure which was advanced for the technetium complex.⁽²⁹⁷⁾ The chemical shift of the proton on the carbon next to the COOH group in sodium gluconate (in D_2O) was 4.12 - 4.14 ppm from the internal standard, and in the

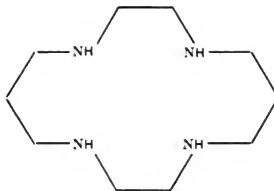
Tc(V)-glucoheptonate solution it was at 4.36-4.38 ppm. The change was attributed to the presence of the paramagnetic Tc(V) in the complex, operating as a shift reagent. However, Tc(V) is diamagnetic,³⁰¹ like Re(V),²⁵¹ and hence cannot function as a shift reagent. The shift may be due to a different cause. The Tc-glucoheptonate solutions in this work appeared to be acid. The shift could have been caused by protonation of the carboxylate group. Sawyer and Brannon found that acidifying a sodium gluconate solution produced a shift in the proton on the carbon alpha to the carboxyl group; it went from 1.017 to 1.333 ppm. The four remaining protons did not change frequency to any significant extent.³⁰²

In the structure projected for the Tc-glucoheptonate complex, the charge on the complex was assumed to be -1. This was based on previously published batch equilibration studies of the distribution of ^{99m}Tc activity between an anion-exchange resin in the perchlorate form and a solution of NaClO₄ operating as a displacing electrolyte. The slope of the radioactivity-concentration curve gives the charge on a given complex by comparison with a known compound like NaTcO₄.^{303, 304} However, particularly in the case of anion exchange resins, the species on the column may not be the major species in solution. In studying the uptake of Co(II) salts in HCl solution by a strongly basic anion-exchange resin, Kraus and Moore found that the species [CoCl₃(H₂O)]⁻ was picked up by the resin in preference to the principal species present in concentrated HCl which is [CoCl₄]²⁻.³⁰⁵ In the same vein, it has been reported that a potassium, ammonium or cesium salt comes out of a Tc(V) solution in concentrated HCl as Cs₂TcOCl₅, etc.³⁰⁶ whereas a quaternary ammonium salt comes out as R₄N TcOCl₄.³⁰⁷ The strongly basic anion-exchange resins can be regarded as cross-linked quaternary ammonium compounds. In addition, the charge on the glucoheptonate complex of Tc(V) should have been determined at different pH values, regardless of the method used. The reversible spectral change with pH shown by Tc-glucoheptonate solutions²⁷⁷ most probably means that one or more protons have been added to the complex on acidification. This will change the charge on the complex. According to Sawyer, the Fe(III) gluconate complex (a 1:1 complex in which the COOH group is not directly involved) can assume charges ranging from +2 in acid to -1 in alkaline solution.³⁰⁸

There is an important conceptual difficulty associated with the suggested structure of the Tc(V) glucoheptonate complex. It is assumed that two glucoheptonate ligands react with the technetium at the carboxylate and the alpha-carbon alkoxide groups. However, if this were correct, any alpha-hydroxycarboxylic acid should form similar complexes. Yet lactic and glycolic acids do not form Tc(V) complexes, and glyceric acid which does, disproportionates rapidly in acid solution, unlike Tc(V) glucoheptonate, which merely undergoes a reversible spectral shift. The projected structure does not explain the source of the greater stability of the longer-chain Tc(V) polyhydroxy carboxylic acid complexes in this regard. It appears, then, that the polyhydroxy carboxylic acids form the same alkoxide-based chelate found for the Tc(V) polyhydric alcohols.

D. Compounds of Tc(V) and Nitrogen-Containing Ligands

It has been known for some time that Re(V) forms trans-dioxo complexes with nitrogen bases, both mono- and bi- or poly-dentate. [ReO₂(py)₄]³⁺ Cl⁻ and [ReO₂en]³⁺ Cl⁻ are typical.²⁵¹ In the case of technetium, an early paper by Spitsyn and his collaborators described a dioxo Tc(V) tetrapyridine complex which was characterized by its IR spectrum.³⁰⁹ In addition, the reduction of pertechnetate-^{99m}Tc by SnCl₂ in alkali in the presence of cyclam-macrocylic nitrogen compounds produced technetium complexes.³¹⁰ One ligand in particular - 1, 4, 8, 11-tetraazatetradecane, with 4 nitrogen atoms in a ring, which is capable of forming 4- and 5-membered rings with a central Tc atom did form a



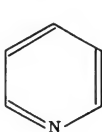
Cyclam

Tc(V) complex. It was free of tin. It was cationic, and had the same electrophoretic mobility as Co(II) cyclam pseudohalide complexes with a + 1 charge, about half the mobility of Ni(II) cyclam complexes with a + 2 charge, and about one-third of the mobility of Co(III) complexes with a + 3 charge. The authors also prepared a Tc-ethylenediamine complex in solution. The same group published the

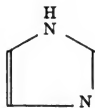


Ethylenediamine

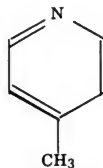
crystal structure of a Tc(V) cyclam perchlorate,⁽³¹¹⁾ which confirmed the conclusions drawn from the earlier chemical work performed on aqueous solutions of the Tc-99m complex. Other Tc(V) complexes with nitrogen bases have been prepared and studied. They include the ethylenediamine complex,⁽³¹²⁾ pyridine, imidazole and picoline complexes,⁽³¹³⁾ and a series of aliphatic amino, heterocyclic and amino-



Pyridine



Imidazole



Picoline

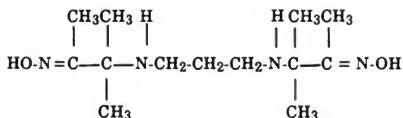
acid ligands which form cationic Tc(V) complexes.⁽³¹⁴⁾ All tetramines which have been studied show the trans-dioxo structure in their Tc complexes. In terms of stability in solution, the cyclam type of

structure appears to be most stable. The ethylenediamine complex decomposes in water unless excess ligand is present. This is also true of the complexes of monodentate ligands.

Diamine complexes of Tc(V) have been prepared with 1,2-propylenediamine⁽³¹²⁾ and 1,3-propylenediamine⁽³¹²⁾ which means that Tc(V) can form both 5-membered and 6-membered rings with two nitrogen atoms.

Zuckman and his collaborators have suggested that dioxo complexes of Tc(V) and Re(V) are formed when the ligands are uncharged and are poor π donors, like the nitrogen bases mentioned above. When the ligands are negatively charged and operate as strong π donors, like oxygen, sulfur and halogen anions, five-coordinate complexes with a $Tc=O$ core are formed.⁽³¹¹⁾ That is, formation of a dioxo core is a means of reducing the effective central charge of the technetium, but this is also effectively done by the above anions.

However, the existence of another type of nitrogen-based ligand complicated this picture. This is the amine-oxime class of reagents. In the reactions with Tc(V), two amino nitrogen atoms are deprotonated on complex formation and the two nitrogen atoms of the oxime groups complete the formation of the complex.⁽³¹³⁾ The OH groups of the two oximes lose a proton, and form a hydrogen bond between them. The complication is that in spite of coordination to four nitrogen atoms, the Tc(V) forms a TcO_2^+ core rather than the expected $trans-TcO_2^+$ core. This emerged after the earlier work which was limited to radiochemical studies with ^{99m}Tc which reacted with 3,3'-(1,3-propanediyl-diimino) bis (3-methyl-2-butanone oxime) (known as PnAO).⁽³¹⁶⁾



PnAO

These radiochemical studies by Troutner and his collaborators showed that the complex was neutral and lipophilic.⁽³¹⁷⁾ Crystals of the Tc-PnAO were then prepared with ^{99}Tc and analyzed.⁽³¹⁸⁾ There was a planar arrangement with the four nitrogen atoms, a shortened oximate-O-oximate-O distance compatible with a single hydrogen bond, a Tc-O distance - 1.679 Å - comparable with other Tc=O distances, and occupying the apical position. More recently, after the discovery that the ^{99m}Tc PnAO complex penetrated the intact blood brain barrier (but was washed out too rapidly for use with a slowly rotating gamma camera), a number of other ligands of this type were synthesized and structures and various properties of their Tc complexes were examined.⁽³¹⁹⁾ The Tc=O distance is a little on the long side (1.676 Å) when compared with those of other complexes (1.61-1.67 Å). The IR stretches for Tc=O range from 908-923 cm^{-1} . The average Tc-N_(amide) bond is 1.913 Å; typical Tc-N_(amine) distances are 2.088-2.259 Å. The authors concluded that the two deprotonated N atoms show sp^2 rather than sp^3 hybridized character. This, together with the deprotonation of the amine groups makes the TcO_2^+ core more stable than a $trans-TcO_2^+$ species, which in any event may be geometrically difficult to form, given the steric crowding of the Tc=O by methyl groups on the carbon atoms adjacent to the amide nitrogens.

A further investigation by the same group shifted the inquiry from the effects of substituent charge on the backbone to a study of the effects of changing the lengths of the hydrocarbon backbone itself.^(319a) The backbone groups^(319b) were: ethylene (En), propylene (Pn), butylene (Bn) and pentylene

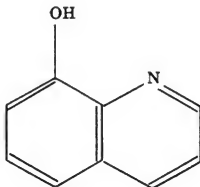
(Pent). The prototype is the original $\text{Pn}(\text{AO})_2$, commonly called PnAO .^[316] This work turned up both monoxo ($\text{Tc}=\text{O}$) and dioxo ($\text{O}=\text{Tc}=\text{O}$) cores. In addition, there was an unusual 8-membered chelate ring with a $\text{Tc}(\text{V})$ center in $\text{TcO}_2 \text{Pent}(\text{AO})_2$, (with no backbone), $\text{TcOEn}(\text{AO})_2$ showed a $\text{Tc}=\text{O}$ stretch at 930 cm^{-1} , like Tc-PnAO . However, the Bn and Pent complexes showed stretches at 790 cm^{-1} , consistent with either a Tc dimer or $\text{O}=\text{Tc}=\text{O}$. The $\text{TcO}_2 \text{Pent}(\text{AO})_2$ was approximately octahedral, 6-coordinate. The Tc was in the plane of the nitrogen atoms, not above it as in TcPnAO . One oxime hydrogen was lost in the complexing, but none was lost from the nitrogen atoms. The neutrality of the complex was assured by the additional oxide ion, forming a TcO_2^+ core. The lipophilicity decreased as one went to the $\text{Bn}(\text{AO})_2$ and $\text{Pent}(\text{AO})_2$ complexes --probably because of the introduction of additional oxide ions.

The authors concluded that the only variant in these experiments was the amine-amine backbone length, and hence the overall ring size on complex formation. Davison and Deutsch had suggested that the electronic nature of the groups cis to the oxo groups is the primary factor in deciding whether TcO^{3+} or TcO_2^+ will form. Anions will help to stabilize the TcO^{3+} core by reducing the effects of the central charge. Thus, an amide will lose a proton, forming an amido anion and will show sp^2 character, and (from the decrease in the Tc-N distance) will show multiple bond formation-factors which stabilize TcO^{3+} . However, with the longer backbone, steric constraints become very important and too great a Tc-N distance will result in TcO_2^+ formation, the N atoms will retain sp^3 character with their hydrogen, and they will behave like hard, neutral donor atoms. The increased ring size introduces too much strain for the deprotonation of the amino group, forcing long Tc-N distances.

Overall, more stabilization is obtained through deprotonation and sp^2 hybridization of amine nitrogens, and through formation of Tc-N multiple bonds (as with $\text{Tc}(\text{V}) \text{PnAO}$) than is achieved by formation of the trans-dioxo species TcO_2^+ .

E. Mixed Nitrogen-Oxygen Complexes of $\text{Tc}(\text{V})$

8-Hydroxyquinoline represents a type of reagent which can form mixed nitrogen-oxygen

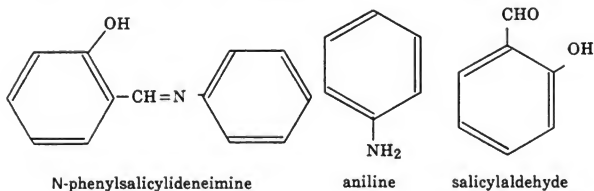


8-Hydroxyquinoline

complexes with $\text{Tc}(\text{V})$, in which there are two coordinating sites on the same molecule. At present several different oxinate complexes have been reported. Rajec and Mikulaj claimed that they had prepared $[\text{TcO}_2(\text{OX})(\text{H}_2\text{O})_2]$ (here OX represents the oxinate anion of 8-hydroxyquinoline).^[320] It was made by treating a concentrated HCl solution of pertechnetate-99 (thereby producing TcOCl_4^-) with

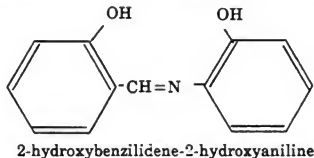
oxine and repeatedly extracting excess oxine. Their analysis showed almost a 1:1 ratio of technetium to oxine, and an IR band close to that reported earlier for a Re(V)-oxinate .⁽³²¹⁾ In the latter work, $\text{ReO}_2 \cdot 2\text{H}_2\text{O}$ was melted with excess 8-hydroxyquinoline in air. Two products were obtained - a green compound with a 1:1 ratio of rhenium to oxine, and a 1:2 compound. Both products showed an IR peak at 920 cm^{-1} , and both in solution showed a band near 415 nm . This was also the case for the Tc-oxinate compound reported by Rajec and Mikulaj. The one disconcerting assignment in both papers is that of the IR stretch at 920 cm^{-1} to either ReO_2^- or TcO_2^- . Wilcox, Haig and Deutsch reacted a number of substituted 8-hydroxyquinolines with a TcOCl_4^- salt in methanol, and obtained and characterized compounds which unambiguously had two moles of oxinate for each mole of technetium, and showed an IR band whose frequency was well above 900 cm^{-1} .⁽³²²⁾ They also carried out a crystal structure analysis of one of the complexes. The compounds had the general composition $[\text{OTc}(\text{Ox})_2\text{Cl}]$; the 8-hydroxyquinolate complex had a peak at 404-nm , with a molar absorptivity of $9600\text{ M}^{-1}\text{cm}^{-1}$. This is somewhat greater than the value reported by Rajec and Mikulaj: $\lambda_{\text{max}} = 405\text{ nm}$, $\epsilon = 6650\text{ M}^{-1}\text{cm}^{-1}$. On the other hand, a different complex was found by Hwang and Steigman.⁽³²³⁾ They carried out a spectrophotometric mole-ratio study of the reaction between TcOCl_4^- (prepared from NH_4TcO_4 in concentrated HCl) and 8-hydroxyquinoline in 8 molal tetra-*n*-butylammonium bromide or 29 molal choline chloride. The quaternary ammonium salts stabilized the TcOCl_4^- anion against hydrolysis, and also salted in both the oxine and any oxinate complex. In these systems a compound was formed with an absorption maximum at about 532 nm with a molar absorptivity coefficient of $2300\text{ M}^{-1}\text{cm}^{-1}$, and the composition of this complex was 1:1 technetium to oxine. They also prepared a solution of Tc(V)-gluconate in alkali by reduction with SnCl_2 , neutralized the preparation to pH 7 in the same quaternary ammonium salt solutions, performed mole-ratio studies with 8-hydroxyquinoline, and found the same spectrum as before, and the same 1:1 stoichiometry in the complex. While no crystalline product was obtained, nevertheless a complex was prepared in homogeneous solution with Tc(V) and 8-hydroxyquinoline with a different spectrum and a different composition from those in the earlier work.

Schiff bases constitute a second and potentially very large type of mixed-atom-ligand for Tc(V) . The bidentate ligand *N*-phenylsalicylideneimine (prepared from aniline and salicylaldehyde)

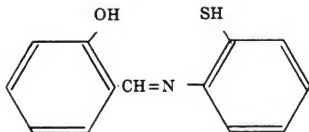


was reacted with $[\text{AsPh}_4][\text{TcOCl}_4]$ in ethanol.⁽³²⁴⁾ Two products were obtained: an intermediate compound with a $[\text{TcOCl}_3\text{L}]^-$ anion (here L represents the anion of the Schiff base) and a neutral complex, $[\text{TcOCl}_2\text{L}]^0$. The structure of the final product was determined. The coordination geometry around the technetium is approximately octahedral. The two ligands (L) are orthogonal to each other, so that one ligand bridges an equatorial and an apical position, and the other occupies equatorial positions. A tridentate Schiff base, similar to the one described above, but with a phenolic group ortho to the nitrogen was prepared by condensing 2-amino-phenol with salicylaldehyde in ethanol.⁽³²⁵⁾ The technetium complex was prepared by reacting $[\text{AsPh}_4][\text{TcOCl}_4]$ in ethanol with the Schiff base. The

resulting uncharged Tc complex is soluble in halogenated organic solvents. The IR $\text{Tc}=\text{O}$ stretch is at 980 cm^{-1} . The structure is a distorted square pyramid with the oxo group displaced by $0.67\text{ \AA}$ out of the basal plane. It is therefore 5-coordinate in the solid state. This was attributed to the ligand requirements. Three tetradentate ligands were prepared from salicylaldehyde and phenylenediamine or ethylenediamine, and from acetylacetone and ethylenediamine.⁽³²⁶⁾ The Tc(V) complexes were prepared by reaction with $[\text{Bu}_4\text{N}][\text{TcOCl}_4]$ in ethanol. X-ray analysis showed that the cationic complex based on the ethylene bis (acetylacetonimineato) ligand had a trans-oxoaquattechnetium(V) core ($\text{O}=\text{Tc}-\text{H}_2\text{O}$). This is an intermediate composition between $\text{Tc}=\text{O}$ and $\text{O}=\text{Tc}=\text{O}$, but showed an IR stretch in the $900\text{--}980\text{ cm}^{-1}$ region, like the other reported in the paper. The ethylene bis salicylideneimine complex was uncharged, with a chloride trans to the $\text{Tc}=\text{O}$ bond. Eight 6-coordinate mixed tri- and bidentate Schiff base complexes of Tc(V) and Re(V) were prepared, and the crystal structure of one of these was determined.⁽³²⁷⁾ The coordination geometry of the subject compound was approximately octahedral. The phenolic oxygen of the quinolinolate was trans to the $\text{Tc}=\text{O}$ bond, whereas the phenolate of the salicyl group was in the equatorial position. A different type of Schiff base was prepared by DuPreez and his collaborators; the compounds included 2-hydroxybenzilidene-2-hydroxyaniline and similar ligands which yielded technetium complexes of the

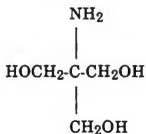


type $[\text{Bu}_4\text{N}][\text{TcO}_2(\text{Schiff base})[\text{TcO}_2(\text{Schiff base})\text{H}_2\text{O}]$.⁽³²⁸⁾ Pertechnetate-99 was reduced in alkaline solution by $\text{Na}_2\text{S}_2\text{O}_4$ in the presence of a ligand, and the product was isolated as the tetra-n-butylammonium salt, and purified by recrystallization. The compounds were characterized by elemental analysis, IR and electronic absorption spectra, and conductivity in nitromethane. It was concluded that these were Tc(V) complexes. These Schiff-base ligands included monoanionic bidentate and di-anionic tridentate compounds. In some cases, sulfur was substituted for oxygen, as in 2-hydroxybenzilidene-2-thiolaniline. The surprising finding was that the TcO_2^- core (the dioxotechnetium(V) core) was present in anions in all cases. In corroboration, the IR stretching frequency for the TcO_2^- group was at or below 800 cm^{-1} . It has been argued that the TcO^{3+} core is found in complexes (often with negative groups bonded to the technetium) in which the ligands can operate as strong π donors, and that otherwise one will find the TcO_2^- core in neutral ligands (like amines).⁽³¹¹⁾ This is not the case here; the authors are reporting TcO_2^- cores in anionic complexes of Tc(V) . They hypothesized that the overall Lewis basicity of the planar ligand systems, rather than the formal charge of the accompanying planar ligands is important in determining which core is formed.



2-hydroxybenzilidene-2-thiolaniline

Ethanolamine and other similar alkanolamines form weak complexes with pertechnetate + SnCl_2 in alkaline solution.^[323] It was assumed that these were Tc(V) complexes. While there is a large number of physiologically active substances which offer N, O coordination to technetium, these will probably be quite weak. This is reported here as a warning against using Tris (tris (hydroxymethyl) aminomethane) buffers in solutions containing pertechnetate which is going to be reduced since the buffer may produce an unwanted complex of technetium.



Tris

F. Nitrido Complexes of Technetium(V)

A nitrido complex of technetium(V) was prepared by reacting NH_4TcO_4 with $\text{N}_2\text{H}_4\cdot 2\text{HCl}$ (hydrazine dihydrochloride) in 0.5 M HCl in ethanol in the presence of triphenylphosphine, and with air excluded. The product was $\text{TcNCl}_2(\text{PPh}_3)_2$. It was possible to prepare other nitrido complexes by ligand exchange; this included the diethyldithiocarbamate complex, $\text{TcN}(\text{S}_2\text{CNEt}_2)_2$.^[329] This had also been the method used to prepare the rhenium analog some years before.^[330] Baldas and his coworkers prepared the technetium complex somewhat differently. They reacted NH_4TcO_4 with hydrazine in aqueous 5 M HCl, neutralized and added sodium diethyldithiocarbamate.^[331] The compound was isostructural with the rhenium analog. The $\text{Tc}=\text{N}$ distance was 1.604 Å with the nitrogen in the apical position in a distorted square-pyramidal geometry. The four sulfur atoms formed the base. The $\text{Tc}-\text{S}$ distance ranged from 2.381 to 2.391 Å. The Tc atom was 0.745 Å above the basal plane. A strong IR band at 1070 cm^{-1} was assigned to the $\text{Tc}=\text{N}$ triple bond, on the basis of similar values attributed to the $\text{Re}=\text{N}$ bond.^[332] The carbamate complex was insoluble in water, and soluble in chloroform. A second $\text{Tc}=\text{N}$ complex was prepared by ligand exchange.^[333] NH_4TcO_4 was reduced with hydrazine in HCl in the presence of triphenyl phosphine, and the resulting complex,

$[\text{TcNCl}_2(\text{PPh}_3)_2]$ was reacted with NH_4SCN in ethanol to replace the chloride with thiocyanate, and finally was reacted with acetonitrile. The product had acetonitrile of crystallization as well as coordinated acetonitrile. The structure is a distorted octahedron. The $\text{Tc}=\text{N}$ distance is 1.629 Å, markedly greater than that found for the dithio-carbamate complex, and reminiscent of a large spread in $\text{Re}=\text{N}$ distances.⁽³³⁴⁾ The thiocyanate ions are bonded to technetium through the nitrogen atoms as in other technetium and rhenium thiocyanate complexes.^(23, 335, 336, 337) The $\text{Tc}=\text{N}$ IR stretch is at 1088 cm^{-1} .

A general synthetic method for preparing nitride complexes of Tc(V) by reduction of a Tc(VI) compound was worked out by Baldas and his collaborators. They formed salts of the Tc(VI) complex anion TcNCl_4^- , and reduced the technetium with reagents which could also coordinate it.⁽³³⁸⁾ The preparation and general properties of the Tc(VI) nitrido chloro complexes were described in the section on Tc(VI) compounds. The quaternary ammonium and arsonium salts are soluble in acetonitrile, and react readily with displacement reagents (e.g., bromide replacing chloride) or an excess of reducing ligands: triphenylphosphine, dithiocarbamate salts, thiocyanate, and 8-quinoline thiol (called thiooxine). Thiooxine yielded crystals of the bis (8-quinolinethiolato) nitridotechnetium(V). The crystal structure is a distorted square pyramid. The $\text{Tc}=\text{N}$ bond length is 1.623 Å, the nitrogen atom is at the apex. The two ligands are unusually planar. It was noted that while the chloride ligands were easily hydrolyzed in water, the $\text{Tc}=\text{N}$ grouping was quite stable. This was evidenced by the persistence of the IR band at 1058 cm^{-1} after hydrolysis. Recently, Duatti et al have developed a procedure to prepare Tc(VI) nitrido complexes under mild conditions using derivatives of S-methyl dithiocarbamate.^(339b)

Unlike the TcOCl_4^- and TcOCl_5^{2-} anions which exist in equilibrium in HCl solution,^(345b) the TcNCl_4^- anion is the only one found in solution; TcNCl_5^{2-} is isolable only as a cesium salt in the solid phase. If the salt is dissolved in reasonably concentrated HCl, only the TcNCl_4^- anion is found.^(245c) In more dilute solution, a pink species is formed. As the concentration of HCl is increased, an equilibrium is established between TcNCl_4^- and the pink species. The addition of water to solid $\text{Cs}_2\text{TcNCl}_5$ and of concentrated HCl produces a deep blue species which is converted to TcNCl_4^- on standing. Both the pink and the blue species are diamagnetic.

If $\text{Cs}_2\text{TcNCl}_5$ is dissolved in water, an orange solution forms which turns violet-brown and deposits a brown chloride-free precipitate of nitridotechnetium(VI) acid.^(245d) This shows IR peaks at 1054 ($\text{Tc}=\text{N}$) and at 708 cm^{-1} (probably $\text{Tc}-\text{O}-\text{Tc}$, pointing to its polymeric nature). Drying the solid leaves a residue whose empirical formula is $\text{TcN}(\text{OH})_3$. It dissolves readily in HCl, and will precipitate $\text{AsPh}_4(\text{TcNCl}_4)$ on addition of AsPh_4Cl . It is also soluble in 1M KOH; the addition of HCl produces TcNCl_4^- . When the $\text{TcN}(\text{OH})_3$ is freshly precipitated by cold water, it is soluble in a wide variety of organic and inorganic acids, permitting the preparation of TcN complexes free of chloride.

TcNF_4^- and mixed fluoride-halide complexes are prepared by adding concentrated HF to $\text{Cs}_2\text{TcNCl}_5$. With an excess of AgF , one can produce only TcNF_4^- in HF solution.

Mixed halo-cyano complexes are made by reacting $\text{Cs}_2\text{TcNCl}_5$ or $\text{TcN}(\text{OH})_3$ with aqueous KCN. These are yellow solutions which yield solid $(\text{AsPh}_4)_2\text{TcN}(\text{CN})_4(\text{OH})_2 \cdot 5\text{H}_2\text{O}$, a Tc(V) complex. Addition of concentrated HCl to the yellow cyanide solution changes the color to deep purple, and esr shows three species: TcNCl_4^- , $\text{TcNCl}_3\text{CN}^-$, and $\text{TcNCl}_2(\text{CN})_2^-$. The TcN^{3+} core undergoes oxidation to TcN^{4+} in HCl, possibly by reacting with air.^(245d)

G. Some Additional Compounds of Technetium(V)

1. Thiocyanate Complex

A Tc(V) thiocyanato complex was prepared by reacting $n\text{-Bu}_4\text{NTcOCl}_4$ in iced methanol with ammonium thiocyanate and then precipitating with Ph_4AsCl . A red crystalline solid was formed.⁽³³⁹⁾

This was $(\text{Ph}_4\text{As})_2\text{TcO}(\text{NCS})_5$, characterized by elemental analysis, IR spectroscopy ($\text{Tc}=\text{O}$ stretch at 945 cm^{-1}) and magnetic moment. The compound was dissolved in acetonitrile and treated with excess ammonium thiocyanate with which it reacted slowly undergoing further reduction to form a mixture of $\text{Tc}(\text{NCS})_6^{2-}$ and $\text{Tc}(\text{NCS})_6^{3-}$ - that is, a mixture of $\text{Tc}(\text{IV})$ and $\text{Tc}(\text{III})$.⁽²²⁾ It can be assumed that the technetium is bonded to the nitrogen rather than to the sulfur atoms in the thiocyanate ligand in the $\text{Tc}(\text{V})$ complex, like the bonding in the lower-valent compounds.

2. Cyanide Complexes

Cyanide complexes of $\text{Tc}(\text{V})$ have been prepared in various ways.⁽³⁴⁰⁾ These include a replacement reaction in methanol between NH_4TcCl_5 and KCN , which initially yielded a $\text{Tc}(\text{III})$ complex: $\text{K}_4\text{Tc}(\text{CN})_7 \cdot 2\text{H}_2\text{O}$. On recrystallization in the presence of air, the latter was oxidized to $\text{K}_2\text{TcO}(\text{CN})_5 \cdot 4\text{H}_2\text{O}$. The same compound was prepared by the oxidation of $\text{TcO}_2 \cdot 2\text{H}_2\text{O}$ in the presence of KCN . The $\text{Tc}=\text{O}$ stretching vibration of the $\text{Tc}(\text{V})$ complex was at 910 cm^{-1} . The *trans* complex, $\text{TcO}_2(\text{py})_4\text{ClO}_4 \cdot 2\text{H}_2\text{O}$ when treated with KCN in methanol yielded $\text{K}_3\text{TcO}_2(\text{CN})_4$. The $\text{O}=\text{Tc}=\text{O}$ asymmetric stretch was at 785 cm^{-1} . It was also possible to obtain a cyano complex by direct reaction of $n\text{-Bu}_4\text{N}^+\text{TcOCl}_4^-$ with KCN in methanol. The compound was $[(n\text{-Bu}_4\text{N})_2\text{TcO}(\text{OMe})(\text{CN})_4]$. In this complex the $\text{Tc}=\text{O}$ stretch was at 932 cm^{-1} , and the $\text{Tc}-\text{OMe}$ stretches (symmetric and anti-symmetric) were at 1097 and 1460 cm^{-1} .

3. Arsine Complexes

A $\text{Tc}(\text{III})$ arsine complex, $[\text{Tc}(\text{diars})_2\text{Cl}_2]^+\text{ClO}_4^-$ in which diars stands for *o*-phenylenebis(diarsine) was oxidized in alcohol solution by means of Cl_2 .^(341a) This produced an eight-coordinate $\text{Tc}(\text{V})$ complex: $[\text{Tc}(\text{diars})_2\text{Cl}_4]\text{PF}_6$. The new compound possessed dodecahedral coordination.

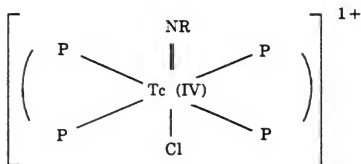
4. EDTA Complex

A seven-coordinate oxo technetium(V) complex with EDTA was prepared as the barium salt by Deutsch and his collaborators. It was synthesized by reacting H_4EDTA with TcOCl_4^{1-} in anhydrous dimethyl sulfoxide, yielding the $\text{Tc}(\text{O})\text{EDTA}^{1-}$ anion as the acid.^(341b)

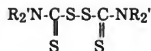
5. A New Type of $\text{Tc}(\text{V})$ Core

It is possible to classify $\text{T}(\text{V})$ compounds by the core containing Tc and another atom. The cores would include: TcO^{3+} , TcO_2^{1+} , $\text{Tc}-\text{O}-\text{Tc}$ (dimer) and $\text{Tc}=\text{N}^2+$ (nitrido). Compounds containing a new core-a Tc -imino core-were recently reported.^(341c) The complexes contain the core $(\text{Tc}^{\text{V}}=\text{NR})^{3+}$ in which NR represents an amino group. The core $(\text{TcNR})^{3+}$ is formally analogous to TcO^{3+} . In one method of synthesis, the salt $(\text{Bu}_4\text{N}^+)(\text{Tc}^{\text{V}}\text{OX}_4^-)$ ($\text{X}=\text{Cl}, \text{Br}$) is reacted with excess RNCO in toluene, producing $\text{Bu}_4\text{N}^+(\text{Tc}^{\text{V}}\text{NRX}_4^-)$. In turn the latter is a good starting material for new $\text{Tc}=\text{NR}$ complexes.

A second synthesis was made by reacting an aromatic amine with $\text{Bu}_4\text{N}^+\text{TcOCl}_4^-$ in the presence of phosphine. If the latter was triphenyl phosphine (PPh_3), the resulting product was $(\text{TcV}(\text{NC}_6\text{H}_4\text{Z})(\text{Cl}_3)(\text{PPh}_3)_2)$. If the phosphine was $\text{R}_2\text{P}-\text{CH}_2-\text{CH}_2-\text{PR}_2$, the product was a $\text{Tc}(\text{IV})$ complex:



The $\text{Tc}(\text{V})$ complex was useful in substitution reactions, for example, displacing two of the three halogens with



The complex itself was structurally characterized.

H. Displacement Reactions and Mixed-Ligand Complexes of $\text{Tc}(\text{V})$

Displacement reactions have been used in the synthesis of many $\text{Re}(\text{V})$ and of some $\text{Tc}(\text{V})$ complexes. One group of compounds - TcOCl_4^- and TcOBr_4^- salts - have been used in a number of syntheses which were described earlier. The solid salts (usually quaternary ammonium or arsonium compounds) have been characterized structurally and show the pyramidal structure of oxotechnetium(V) compound. Perhaps the simplest synthesis is that reported by Bandoli et al.⁽³²⁴⁾ $\text{AsPh}_4\text{AsTcO}_4$ was precipitated from aqueous solution, reduced with concentrated HCl and recrystallized from a methylene chloride pentane mixture. Displacement reactions with these anions cannot be used in water because of rapid solvolysis and disproportionation.⁽³⁰¹⁾ The displacements are usually carried out in methanol or ethanol.

Steigman and his collaborators introduced the use of $\text{Tc}(\text{V})$ polyhydroxy compounds, including the gluconate, as intermediates in the preparation of more stable $\text{Tc}(\text{V})$ compounds in water by displacement reactions. Equal moles of pertechnetate and SnCl_2 were reacted in alkali in the presence of excess sodium gluconate to form the $\text{Tc}(\text{V})$ complex, and after pH adjustment a second ligand, like cysteine, was added to the solution.⁽³²⁴⁾ This procedure was used by Spies, Johannsen and Muenze in preparing a large number of $\text{Tc}(\text{V})$ complexes (mostly dithiols).⁽³⁴⁷⁾ Probably any labile complex of $\text{Tc}(\text{V})$ can be used in this way.

There is one aspect of complex formation by displacement: the formation of intermediate complexes, that is, of mixed-ligand complexes. Such complexes have been found in the reactions of

Tc(V) - polyol complexes. The addition of DTPA to an alkaline solution of the Tc(V) ethylene glycol complex produces no change in the visible absorption spectrum. However, on acidification (pH < 6) the band near 500 nm disappears, and a new peak at 620 nm is seen.^[343] The change is reversible with change of pH. No disproportionation is seen, although the Tc(V) - ethylene glycol complex in water rapidly forms TcO₂ and TcO₄⁻ on acidification. A more quantitative spectrophotometric study of the reaction between DTPA and the Tc(V) - mannitol complex showed that one DTPA displaced one mannitol from the original complex. At room temperature, the equilibrium constant for the consumption of one DTPA and the release of one mannitol was 188 ± 22 .^[323] The gluconate complex behaved like the other polyhydric complexes. Glycine reacted like DTPA with the polyhydric complexes.

This work was recently confirmed and extended by Linder, who reacted the crystalline sodium Tc(V) ethylene glycol complex with various amino-carboxylate ligands.^[344] One important question was settled, among others: the addition of an aminocarboxylate ligand to either Tc(V) glycol complex or the corresponding gluconate complex was by way of nitrogen-technetium bonds, and did not involve any carboxylate groups.

One somewhat puzzling aspect of these mixed complexes is that while the ethylene glycol complex is formed in alkali and decomposes in quite dilute acid, and amine complexes would be expected to form more readily in alkali and also decompose (by protonation) in acid, the mixed complexes show no sign of formation (in water) except in acid solution.

I. Binding of Tc(V) Compounds to Plasma

Dewanjee and his co-workers studied the binding of various technetium compounds to human serum albumin, using both sequential and equilibrium dialysis.^[80] They prepared solutions with different concentrations of ^{99m}Tc chelates (with ^{99m}Tc as the tracer) and a fixed concentration of albumin. Equilibrium dialysis proceeded from 4 ml of radioactive solution into 13 ml of N₂-purged saline solution. Binding constants were calculated from a modified Scatchard plot. Two Tc(V) complexes were examined: Tc(V) glucoheptonate, and a dimercapto-succinate complex (which is probably a mixture of complexes).^[345] Parallel experiments with no-carrier-added ^{99m}Tc preparations showed that technetium was strongly adsorbed by the cellulose tubing in the absence of albumin: 46% for the DMSA complex, and > 23% for the glucoheptonate. By adding enough albumin, they were able to reduce the adsorption to 12.5% and 6.3% respectively. With the glucoheptonate, in the absence of albumin, about 70% of the activity came through the membrane, the interior held 1.4%, and the tubing had adsorbed 29%. In the presence of albumin, the interior solution held 23%, adsorption on the walls was reduced to 6%, and 70% of the activity again came through to the outside solution. The following question arises: If albumin does not penetrate the cellulose tubing, should not the outside of the tubing show heavy adsorption of technetium - unless the chemical form of the technetium is changed? In any event, with the glucoheptonate complex one would expect adsorption by any polyhydroxylic surface, like Sephadex or cellophane tubing. An additional problem is that of labeling albumin with ^{99m}Tc by ligand exchange. Glucoheptonate and gluconate complexes have been used for such a purpose;^[323] this will be discussed in more detail in the section on ^{99m}Tc Chemistry. Another problem, which arises in the case of mercapto ligands, will be discussed below.

Equilibrium dialysis measurements and gel filtration separations were carried out by Johansson, Berger and Schomaecker^[79] on a group of Tc(V) complexes at 20°C in 6.4% human serum albumin buffered by phosphate at pH 7.4. The results were reported as % bound technetium. There is no mention of adsorption of technetium by the membrane except for a no-carrier-added preparation of ^{99m}Tc-DMSA. Cysteine, thioglucose and racemic DMSA showed 6, 17 and 16% binding to albumin. Other preparations, including cysteine ethyl ester (49%), N-acetyl cysteine (84%) and meso DMSA (66%) showed greater binding. Thiolactate and dimercaptosuccinate dimethyl ester showed almost complete binding. The previous research had found the glucoheptonate complex to be bound to albumin to the extent of 29%.^[80] The present research found 85% of the technetium bound to the

albumin. In addition to the problem of labeling albumin with technetium by exchange, there is a second problem in the interpretation of both sets of results which comes from the presence of excess mercaptan-bearing ligands. Molecules like cysteine and DMSA are reducing agents, and will reduce proteins like albumin at the disulfide bonds.⁽³⁴⁸⁾ This will form free SH bonds on the albumin, and provide sites for strongly binding technetium.⁽²²³⁾ The extent to which this may happen cannot be predicted at this stage. This question will also be treated in more detail in the section on ^{99m}Tc .

VIII.

Technetium (IV) Compounds

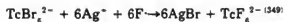
A. Halide Complexes and Oxide of Tc (IV)

Complexes of ^{99}Tc (IV) of radiopharmaceutical interest have been produced in the following ways: by the reaction of pertechnetate with a reducing agent in the presence of a ligand, by the coulometric reduction of pertechnetate in the presence of a ligand, by ligand displacement reactions on hexahalide complexes of Tc (IV), and by reaction between a ligand and precipitated $\text{TcO}_2 \cdot x\text{H}_2\text{O}$ after dissolution of the oxide in acid.

1. Halide Complexes

a. Preparation

Three of the four hexahalide complexes of Tc (IV) have been used in syntheses of various Tc (IV) compounds by displacement. The hexafluoride anion, TcF_6^{2-} , is different from the other hexahalide complexes in that it resists hydrolysis, and undergoes substitution reactions with difficulty. It has been prepared by reacting salts of TcCl_6^{2-} or TcBr_6^{2-} with KHF_2 in a melt.^{(347), (348)} It has also been made by reacting a hexabromide salt with silver fluoride in concentrated HF:



K_2TcCl_6 can be prepared by prolonged heating of KTcO_4 in concentrated HCl .⁽³⁵⁰⁾ A more rapid reduction takes place if either KI ⁽³⁵¹⁾ or H_3PO_2 ^(352;353;354) is added to the acid. The added KI first produces a red crystalline precipitate, identified as $\text{K}_3(\text{TcCl}_6\text{OH})$. This dissolves with difficulty in concentrated HCl to give K_2TcCl_6 .⁽³⁵⁵⁾ It is also possible to obtain an aquo complex from the hydroxo compound.

K_2TcBr_6 has been made by repeatedly evaporating K_2TcCl_6 with concentrated HBr .⁽³⁵¹⁾ or by the direct action of cold concentrated HBr on a pertechnetate salt.⁽³⁵⁶⁾ Salts of the TcCl_6^{2-} anion have been prepared by repeatedly digesting a hexabromo salt with concentrated HCl .⁽³⁵¹⁾

b. Physical - Chemical Properties

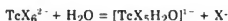
Alkali metal salts of the four halo-complexes, TcX_6^{2-} , show cubic symmetry;⁽³⁵⁷⁾ some show secondary structural complications,^(358,359) as does the pseudo-halide tetraphenylarsonium hexakis (isothiocyanato)technetate (IV) dichloromethane (1/1).⁽³⁵⁹⁾ Their electronic spectra have been analyzed

in great detail.^{353,355,360} Their magnetic moments at room temperature are close to the spin-only value for d^3 complexes that is, 3.88 B.M., but are generally higher than the theoretical value.^{352,361}

The d^3 electronic configuration of monomeric $Tc(IV)$ complexes would suggest that they would show a high degree of kinetic inertia, like $Cr(III)$ compounds.³⁶² However, it is well known that the hexachloro³⁶³ and hexabromo³⁶⁴ complexes hydrolyze in water fairly rapidly, ultimately yielding a precipitate of hydrated TcO_2 .

A photochemical decomposition in aqueous acid solutions of the hexachloro complex has been claimed to occur even in 6 N HCl .^{356,365a,365b} These photolytic reactions, which are induced by both UV and visible light, ultimately reach an equilibrium whose position depends on both the acid concentration and the light intensity. It was hypothesized that the first step in the reaction series was the production of $(TcCl_5OH_2)^+$, the pentachloro-aquotechnetate (IV) complex, followed by the formation of a diaquotetrachloro complex. After this step, cationic and neutral unidentified products appeared. It was claimed that a salt of $(TcCl_5(H_2O))^+$ was separated by ion-exchange chromatography from the starting compound and other products. It was also claimed that when a $TcCl_6^-$ salt in solution was kept in the dark its spectrum showed no change in time in HCl solutions whose concentrations were varied from 0.025M to 11.8M. This is in contradiction with the paper by Boyd who reported that spectral changes were observed after 24 hours even in 3 M HCl .⁽³⁵⁷⁾

The aquation reactions of $TcCl_6^{2-}$ and $TcBr_6^{2-}$ compounds were studied in the dark at 75° or higher for the chloro-complex and at 40° and higher for the bromo compound, in 4.0 molar solutions of chloride and bromide containing different proportions of acid and alkali metal cation.³⁶⁶ The reactions were believed to be simple substitution reactions:



The kinetics were first-order, with half-lives of several hours or less. In the chloride system, it was possible to substitute lithium ions for hydronium ions between 1M and 4M acid with no difference in overall effects. However, the introduction of sodium or potassium ions markedly increased the extent of aquation. The spectrophotometric measurements showed two distinct species with an isosbestic point. It was assumed that two species were in equilibrium: the hexahalide complex, and the pentahaloaquo complex. $TcCl_6^{2-}$ showed an absorption maximum at 340 nm; $\epsilon = 11,040 \text{ M}^{-1} \text{ cm}^{-1}$ and $[TcCl_5 \cdot (H_2O)]^-$, at the same wavelength had an absorptivity coefficient of 6160. For $TcBr_6^{2-}$ and $[TcBr_5 \cdot (H_2O)]^-$, the maximum was at 445 nm. The absorptivity coefficients were $5720 \text{ M}^{-1} \text{ cm}^{-1}$ and $3900 \text{ M}^{-1} \text{ cm}^{-1}$ respectively. The species were separated from one another by ion-exchange chromatography. As long as the total chloride concentration was greater than 3M, equilibrium was maintained. Below that concentration additional changes were observed in the spectra, which no longer showed an isosbestic point. In this connection, the appearance of an isosbestic point in a series of spectra of compounds, related to one another is a necessary but not sufficient condition for the presence of only two species in equilibrium with each other. The calculated equilibrium constants for the aquation reactions were: 1.25 at 75° and 1.39 at 90° (solvent 4M HCl) and 0.76 at 40° and 1.14 at 54.5° in 4M HBr .

There have been additional studies of aquation of the hexachlorotechnetate (IV)^{367,368a} and of the hexabromo-technetate (IV).^{368b,369} However, there is not yet a complete detailed account of the hydrolysis of any hexahalotechnetate (IV) to $TcO_2 \cdot xH_2O$.

The hexahalotechnetates, particularly the chloro and bromo compounds, have been used in displacement reactions with various ligands in the synthesis of many $Tc(IV)$ complexes. These preparations have been most successful when they were carried out in non-aqueous solvents. If they are run in water there may be hydrolysis accompanying the displacement reaction with attendant complications (TcO_2 formation, mixed complex formation, etc.). In any solvent there is the possibility of other complications: oxidation (by air) to a higher oxidation state, or reduction by the ligand to a

lower oxidation state. There should be some independent verification of the valence of the technetium in the complex. It cannot be assumed that the final oxidation state of the technetium in a compound is the (IV) state because one started with a Tc (IV) hexahalogenate.

2. Oxide of Tc

a. Preparation

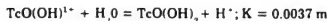
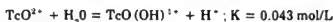
Hydrated $\text{TcO}_2 \cdot x\text{H}_2\text{O}$ has also been used in the synthesis of Tc (IV) compounds. The oxide has been prepared by the electrolytic reduction of pertechnetate in alkaline solution,³⁷⁰ by the reduction of pertechnetate using zinc in HCl ³⁵² by the action of hydrazine on pertechnetate³⁵⁰ or by the hydrolysis of K_2TcCl_6 ³⁵² and K_2TcBr_6 . However, there are no standardized and universally accepted methods of synthesizing $\text{TcO}_2 \cdot x\text{H}_2\text{O}$. Thus, Nelson, Boyd, and Smith reported that the reduction of pertechnetate by zinc in HCl to hydrated TcO_2 was quantitative.³⁵² However, Schwachau and Herr maintained that in this reduction some 20% of the technetium was reduced to metal.³⁷¹ They preferred to prepare the oxide by hydrolysis of the hexachloro complex. On the other hand, Colton and Tomkins reported that a purer product was obtained from the hydrolysis of the hexaiodo compound, because too much cationic impurity was incorporated in the product of hexachloro-pertechnetate hydrolysis.³⁷²

Solid anhydrous TcO_2 , like ReO_2 , has the MoO_2 or rutile structure. It is weakly paramagnetic.

b. Physical - Chemical Properties

The behavior of hydrated TcO_2 in water is not well understood. An early report said that it did not deposit (electrolytically) on platinum from 2M NaOH containing 10^{-6}M pertechnetate, but did so from 10^{-4}M solution.³⁷⁰ This may have been due in part to complex formation in the alkaline solution, since TcO_2 has been reported to dissolve in concentrated NaOH, forming an orange complex (with absorption at 410nm).³⁷¹ TcO_2 was found to dissolve to a limited extent in hot 6M NaOH, the solution was light orange in color, with an absorption maximum at 485 nm.³⁷³ It was also possible to produce a solution of Tc (IV) in 20 M NaOH by the reduction of pertechnetate by SnCl_2 .³⁷⁴ The absorption maximum of this solution was near 490 nm. Boyd et al reported that whereas the reduction of pertechnetate to TcO_2 by zinc in HCl was quantitative within a little more than one hour, reduction by zinc in 2M NaOH (i.e. the appearance of precipitate) was very much slower in spite of the more negative reduction potential of the zinc.³⁷⁵ This is consistent with the formation of a soluble anionic polyhydroxy complex of technetium.

The condition of $\text{TcO}_2 \cdot x\text{H}_2\text{O}$ in aqueous solution was investigated by Gorski and Koch.³⁷⁶ This material was prepared by the hydrazine reduction of pertechnetate, and was subsequently dissolved or dispersed in dilute perchloric acid. The concentration of technetium was not given. They measured its electrical mobility through a column of sea sand, in perchloric acid solutions whose pH ranged from 1 to 2.5. Above pH 2.3 there was virtually no motion of the technetium in the field, suggesting that the charge was zero. The mobility at pH 1.3 was roughly twice that at pH 2.2 (that is, it decreased sharply in that interval) and decreased sharply again after pH 2.2. From this it was concluded that hydrolysis was taking place in two steps, for which equilibrium constants were calculated:



Noll, Seifert and Muenze studied the electrophoresis of $\text{TcO}_2 \cdot x\text{H}_2\text{O}$ dissolved initially in 1M HClO_4 .³⁷⁷ Their apparatus was somewhat more conventional than that of Gorski and Koch, and they used small glass spheres in place of sea sand. They were unable to reproduce the results reported by Gorski and Koch. They concluded that the reported hydrolytic equilibria did not exist, at least on the

basis of electrophoretic and pH-titrimetric measurements. Dialysis measurements showed that there was colloidal matter present in solution until acidities of the order of 1M or higher in HClO_4 were reached.

Sundrehagen attempted to repeat the Gorski and Koch experiment in an apparatus similar to theirs, but reported no success.^{137b} He observed electrophoretic migration of technetium which changed sign in time (and possibly oxidation state as well). He analyzed possible equilibria in dispersed or dissolved $\text{TcO}_2 \cdot x\text{H}_2\text{O}$ in HClO_4 by spectrophotometry, measuring the absorbance of solutions at 210 nm and at 250 nm in 0.028M HClO_4 with added NaClO_4 to maintain constant ionic strength. He assumed that there was a monomer $\text{TcO}(\text{OH})_2$, a dimer $(\text{TcO}(\text{OH})_2)_2$, and a protonated monomer, $\text{TcO}(\text{OH})^{1+}$. He further assumed that at higher technetium concentrations ($> 10^{-5}\text{M}$), only the dimer was present. On this basis he used a chi-square error-minimizing computer program for calculating a dimerization constant ($314 \times 10^{-6}\text{M}^{-1}$), a dissociation constant for the protonated form ($9.3 \times 10^{-3}\text{M}$), and the molar absorptivity coefficients of the three hypothesized species. However, from the work of Noll et al.,^{137c} one would have expected colloid formation in these solutions, and this would have increased the absorbance of solutions because of light scattering, especially at the higher technetium concentration and the shorter wave-length in the UV. In addition, the choice of 210 nm as a wavelength for absorbance measurements was arbitrary, since there was no observable peak at this wavelength in 0.05M or 0.028M HClO_4 . Finally, there was no independent chemical or physical basis for identifying the hypothesized species, and the fitting of data points to the hypothesis does not in itself mean that the calculated quantities represent real properties of real chemical species.

There is possible confirmation of the hydrolysis mechanism of Gorski and Koch in the work of Owunwanne et al.^{137d} These workers studied the exchange reactions between TcO_2 in HClO_4 and $\text{Sr}(\text{ClO}_4)_2$ on a cation-exchange resin, and measured the distribution of the technetium species as a function of $\text{Sr}(\text{ClO}_4)_2$ and acid concentrations. A plot of the log of the distribution coefficient (defined as the ratio of activity in 1g dry resin/activity in 1g solution) against pH gave a 2.18 slope in the pH interval 1.1 to about 2.0. This was interpreted as a charge of 2^+ on the technetium (assuming that the species in solution was the same as that on the resin). A similar plot against the log of the $\text{Sn}(\text{ClO}_4)_2$ concentration showed a 0.98 slope; this was interpreted to mean that the charge on the stannous ion was the same as the charge on the technetium. However, according to Gorski and Koch, from pH 2.3 to pH 1 or so, the charge on the dissolved technetium should increase from 0 to 2^+ . There is no indication of charge variation in that pH interval in the ion-exchange work. That is, the slope of the curve of the log of the distribution coefficient against pH should be changing drastically in that pH interval. It does not do so. There is a minor problem with the ion-exchange work itself. It was implicitly assumed that the species on the resin was the same as the species in solution. They used a standard Zr (IV) exchange, in their work. However, it has been hypothesized that there is more hydrolysis of zirconium in the resin phase than in solution.^{138b}

A solvent extraction method of determining the nature of TcO_2 in aqueous solution was developed by Guennec and Guilaumont.^{138c} However, the percent of extracted $^{99\text{m}}\text{Tc}$ (IV) (extracted as a complex) was small.

c. Solubility of $\text{TcO}_2 \cdot x\text{H}_2\text{O}$

Any knowledge of the behavior of TcO_2 in aqueous solutions must ultimately depend on well-established determinations of its solubility in water and in dilute acid and alkaline solutions. An extensive research on the solubility of TcO_2 in various aqueous solutions was undertaken by Meyer et al at the Oak Ridge National Laboratory.¹³⁹ They prepared the oxide either by the electroreduction of pertechnetate on platinum, or by the reduction of pertechnetate by hydrazine. They also precipitated TcO_2 from pertechnetate-hydrazine mixtures onto purified sand. Solubilities were determined by measuring the beta activity of ^{99}Tc in solutions which had been in contact with the solid oxide, and had been re-circulated or stirred. Oxygen was removed from these solutions by displacement with argon gas. Nevertheless, pertechnetate was found in varying amounts in all samples. It was quantitatively

determined by extraction with tetraphenylarsonium chloride in chloroform. Tc (IV) in solution was determined by beta counting after removal of any pertechnetate. The pH was varied from 0 to 10. In the pH interval 4 to 10 the solubility of TcO_2 ranged from 8.8×10^{-8} to $9.4 \times 10^{-7} \text{M}$, but most values fell between $1 \times 10^{-8} \text{M}$ and $2 \times 10^{-7} \text{M}$. The reported solubilities were limiting values after exposures to the aqueous solutions of up to 300 hours.

In more acid solutions the measured solubility depended at least in part on the source of the TcO_2 . There was a sharp rise in solubility with decreasing pH. The measured values, however, varied considerably. At pH zero, solubilities from 10^{-7}M to 10^{-4}M were found, depending on the oxide source. Cycling a given oxide sample from acid to alkali did not change the alkaline solubility values much, but bringing them back to the acid side changed the solubility greatly, usually in a decreasing direction. It was hypothesized that the solid $\text{TcO}_2 \cdot x\text{H}_2\text{O}$ was changing structure as a result of the cycling process.

Meyer et al assumed that in the pH interval from 4 to 10 the dissolved Tc (IV) was uncharged, but that the increase in solubility in more acid solutions was probably due to the formation of cationic species (for example, $[\text{Tc}(\text{OH})]^{+}$). However, there is another possible explanation: radiocolloid formation. Early in the history of radiochemistry a number of radioactive nuclides in aqueous solution exhibited colloidal behavior—filterability, lowered diffusion coefficients, anomalous adsorption on solid surfaces—at concentrations far below those predicted from solubility product constants, for the onset of precipitation, and hence of colloid formation.^(283, 284) The phenomenon has been attributed to adsorption on colloidal impurities in the water, as well as to the formation of true colloids. This led to a critical re-examination of the solubility product determinations of water-insoluble salts and hydroxides by Haissinsky.^(285, 286) He found that different solubility determinations of insoluble halides, carbonates, sulfates and other salts were in fair agreement. However, in the case of insoluble sulfides and hydroxides there were very large differences in reported solubilities for even the same sample of a given compound, depending (perhaps) on age, history, prior treatments, etc. Measured solubilities differed from one another by orders of magnitude for the same compound. This led to his conclusion that "one is dealing with polydispersed systems containing ions both simple and complex, and colloidal micelles of various dimensions in a slow state of evolution. The ordinary principles of solubility and solubility product are not applicable."⁽²⁸⁴⁾ This may well apply to TcO_2 in water, especially in mildly acid solution.

B. Polyhydroxy and Hydroxy-Acid Complexes of Tc (IV)

1. Ethylene Glycol

In 1977 it was reported that K_2TcBr_4 in alkaline isopropanol solution reacted with ethylene glycol or glycerol to form a violet complex.⁽²⁸⁷⁾ A similar color was developed if NH_4TcO_4 was reduced by SnCl_2 in aqueous solution in the presence of glycerol. The molar absorptivity for the glycerol complex was $60 \text{ M}^{-1}\text{cm}^{-1}$, and that for the ethylene glycol system was $50 \text{ M}^{-1}\text{cm}^{-1}$, both with absorption maxima at 510 nm. Acidification of the aqueous solutions produced TcO_2 . Auxiliary measurements, including electrophoresis, pH-titrations and distribution studies with labeled glycerol led to the conclusion that the presumed Tc (IV)-glycerol complex was anionic, was composed of two glycerol ligands per Tc atom, and carried a charge of -2.

The spectrophotometric results reported for the aqueous solutions, and the formation of TcO_2 on acidification are very much like those reported by Steigman et al for the lower polyol and polyhydroxylic-acid complexes of technetium.⁽²²⁸⁾ However, this group had shown that the complexes were Tc (V) compounds and that the TcO_2 formed on acidification was due to the disproportionation of Tc (V) complexes rather than the simple hydrolysis of a weak Tc (IV)-glycerol complex. This suggested that the reaction observed between K_2TcBr_4 and glycerol in isopropanol was not a simple displacement but may have been caused by air oxidation to Tc (V). It was found that bubbling nitrogen through a solution of glycerol in isopropanol and then adding K_2TcBr_4 to the solution did not

produce any color change, but on exposure to air a pink-violet color slowly developed.^(388a) Recently this conclusion has been reinforced by the synthesis of technetium (IV) alcoholate complexes by Alberto et al.^(388b) These workers reacted K_2TcBr_6 with potassium methoxide in methanol obtaining the pale green $K_2Tc(OCH_3)_4$. In turn this compound was reacted with ethylene glycol and with 1,2,4 butanetriol; the two polyhydroxy complexes were colorless. Each complex in solution (CH_3OH) showed an absorption band in the UV, near 270 nm. The methoxide complex on exposure to air turned red before final oxidation to pertechnetate. The two polyhydroxy complexes were not examined in this way.

2. Citrate

It was reported in the Tc (V) section that a $3.4 \times 10^{-4}M$ solution of pertechnetate in 0.4M citrate at pH 7 undergoes a rapid reduction to the Tc (V) state when $SnCl_4$ ($2 \times 10^{-3}M$) is added.⁽³⁵²⁾ There is a much slower subsequent reduction to Tc (IV) from Tc (V) in this particular solution (initial ratio of Sn/ Tc = 6). The slow step required several hours at room temperature for its completion. No spectrophotometric measurements were carried out on the final solution, but no color development was noted.

Muenze and Grossman reacted K_2TcBr_6 with citrate in water at pH 7.⁽³⁸⁹⁾ They found some TcO_2 , and some compounds which appeared to be interconvertible during pH titrations. The initial reagent concentrations were $2.88 \times 10^{-4}M$ K_2TcBr_6 and $9.65 \times 10^{-3}M$ citrate. One of the products had a deep violet color. It was crystallized from methanol. Its molecular weight was in the range 721-750. It was believed to be $K_4[Tc(OH)(cit)_2] \cdot H_2O$; here the symbol cit stands for the citrate anion, with a -4 charge. Its equivalent conductivity at 25° was $142 \text{ ohm}^{-1}\text{cm}^{-1}\text{vol}^{-1}$. This is, however, difficult to interpret in structural terms, since on the one hand the conductivity of an anion with a -6 charge would be very high, and at the same time a -6 charge would lead to a very high degree of ion-pair formation.⁽³⁹⁰⁾ A similar synthesis was carried out later with larger quantities of reagents.⁽³⁹¹⁾ K_2TcBr_6 was added to citric acid in water, and the pH was raised to 6 with NaOH. A red-brown solution was formed which turned deep violet after several hours of heating. Black-violet crystals were finally obtained. Chromatography of an aqueous solution of this material was carried out with water on Sephadex G-10, yielding a brown substance in the void volume (a polymer). Its basic formula was $Na_2Tc(OH)_2(cit)$. The violet compound was eluted after the brown. Its molecular weight, determined by osmometer, was 1680. The IR spectrum showed no Tc-OH or Tc = O bands (at 1000-1200 and 900-1,000 cm^{-1} respectively), but it did have bands at 724 and 486 cm^{-1} , which were attributed to bent Tc-O-Tc bonds.⁽³⁹²⁾ The formula of the solid was given as $Na_2Tc_2O_4(cit)_2 \cdot 10H_2O$. The magnetic moment was 1.2 B.M., far below the 3.88 spin-only value for a d^5 octahedral species.⁽³⁹¹⁾ An A.C. polarogram showed three consecutive reversible electron steps:



The deep violet color was virtually discharged by the addition of $SnCl_4$ and was restored when iodine was subsequently added to the solution. This was interpreted as a reduction to Tc (III)-citrate, and re-oxidation to the violet Tc (IV) complex.⁽³⁹³⁾ A polarographic study of the reduction of pertechnetate by Sn (II) in the presence of citrate was carried out over the pH interval 2.05 to 9.90.⁽³⁹⁴⁾ There were two complicated reduction waves. AC polarography showed that there were at least four electrode reactions. Contrary to the earlier cited reaction between K_2TcBr_6 and citrate which yielded a deep violet compound, the reduction of Tc (V) in citrate gave a colorless solution. Muenze and Hoffman later confirmed the absence of a deep violet color in the reduction of pertechnetate by excess Sn (II) in the presence of citrate,⁽³⁹⁵⁾ in agreement with the earlier finding by Steigman et al.⁽²⁵²⁾

The deep violet compound resulting from the reaction of K_2TcBr_6 with citrate in water has a low magnetic moment (1 BM).⁽³⁹¹⁾ This contrasts with the behavior of Tc (IV) citrate formed by the reaction of pertechnetate with excess Sn (II) in a citrate buffer at pH 7.⁽³⁹⁶⁾ The magnetic moment in this case was measured by Evans' method, using the proton NMR shift of t-butanol in D_2O solution in

the presence of paramagnetic substances.⁽³⁹⁷⁾ The Tc (IV)-citrate complex showed the same displacement per mole of technetium as Na_2TcCl_4 in concentrated HCl. The latter shift was taken as the displacement to be expected from a d^3 technetium. In contrast, Tc (V) citrate produced practically no shift. It can be concluded that the Tc (IV) citrate complex which is produced by the Sn (II) reduction of pertechnetate in a pH-7 citrate buffer is not a linear technetium dimer or a linear -Tc-O-Tc-type of polymer since such a structure would markedly diminish or eliminate any magnetic moment, as it does with the corresponding Re (IV) compounds.⁽³⁹⁸⁾

3. Carboxylic Acids

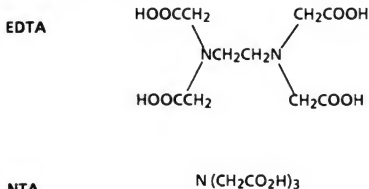
Grossman and Muenze studied the reaction of K_2TcBr_6 with various carboxylic and hydroxycarboxylic acids in water.⁽³⁹⁹⁾ They used spectrophotometry, electrophoresis, and chromatography. They found that in the presence of unsubstituted di- and tricarboxylic acids the TcBr_6^{2-} anion simply hydrolyzed to TcO_2 . The acids included succinic, glutaric, aconitic and tricarballic. With hydroxy acids like tartaric, malic and gammahydroxybutyric, brown to red-violet colors appeared, the relative yields depending on the Tc/ligand mole ratio. Brown components, as with citric acid as ligand,⁽³⁹¹⁾ appeared in the void volume of a Sephadex G-10 column elution, followed by the red-violet species. Again, as with citric acid these brown and violet substances were not formed by the reduction of pertechnetate in the presence of the various ligands.

The possibility must be considered that the use of K_2TcBr_6 in water as a source of Tc (IV) complexes may be accompanied by partial hydrolysis and polymerization, with peptization or partial complex formation with the desired ligand. The oxidation state may be difficult to define-there may be both Tc (IV) and Tc (V) present in a small colloidal particle, stabilized by the ligand.

C. Aminocarboxylate Complexes of Tc (IV)

The first synthesis of a Tc (IV)- amino carboxylate complex was reported by Ziolkowski et al.⁽⁴⁰⁰⁾ A previous paper had described the syntheses of a number of Re (IV) complexes, including an EDTA complex.⁽⁴⁰¹⁾ The rhenium complex served as a carrier for the technetium complex, with the result that the mixed complex had both elements in compounds like $\text{K}_4\{[\text{Re},\text{Tc}] \text{O}(\text{OH})_2(\text{EDTA})_2\}$. Their proportions depended on the solubility characteristics of the pure compounds, as well as on the ratio of the two elements in solution.

The next published account of Tc (IV)-amino-carboxylate complexes came from Gorski and Koch.⁽⁴⁰²⁾ They prepared solutions (or dispersions) of $\text{TcO}_2 \cdot x\text{H}_2\text{O}$ in HClO_4 at pH 1.5-2, and studied the distribution of technetium between a cation-exchange sulfonate resin and solutions containing aminocarboxylate ligands. These included EDTA, NTA and 1,2-diaminocyclohexanetetraacetic acid



(DATA). The last system was also studied by electrophoresis. The assumption was made that reaction occurred between a $(\text{TcO}(\text{OH}))^{1+}$ cation and the fully deprotonated amino carboxylate moiety. Stability constants were calculated according to the methods of Schubert¹⁴⁰³ and Fronaeus.¹⁴⁰⁴ The NTA concentration ranges were recorded: 0.9×10^{-4} to 5.0×10^{-4} M at pH 1.5 and 3.3×10^{-3} to 10.0×10^{-3} M at pH 2. The concentrations of the other ligands and of the technetium were not given.

The methods of Schubert and of Fronaeus are well established, and the formation constants reported by Gorski and Koch represent the magnitude of values one might expect from the behavior of similar complexes. However, the actual existence in solution of the assumed cation $(\text{TcO}(\text{OH}))^{1+}$ and its calculated concentration, as well as its mode of interaction with a cation-exchange resin are not established. The objections raised by Muenze and by Sundrehagen to the characterization of $\text{TcO}_2 \cdot x \text{H}_2\text{O}$ of unknown concentration dissolved or dispersed in dilute perchloric acid apply here as well.

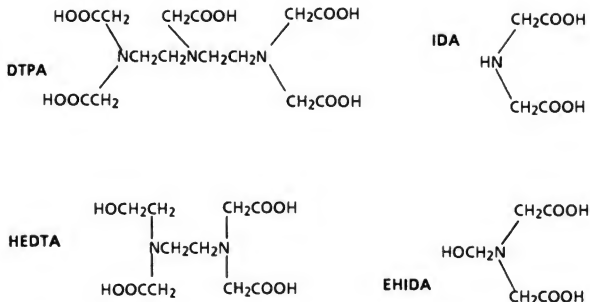
For the record, the given formation constants are:

1. $(\text{TcO}(\text{OH})\text{-NTA})^{2-}$ $\log K_1 = 13.8$, $\log K_{12} = 25.7$
2. $(\text{TcO}(\text{OH})\text{-EDTA})^{3-}$ $\log K_1 = 19.1$
3. $(\text{TcO}(\text{OH})\text{-DATA})^{3-}$ $\log K = 20.7$ or 20.8

Steigman, Meinken and Richards performed a direct potentiometric titration of 4×10^{-4} M TcO_4^- in 0.4 M DTPA at pH 4 with SnCl_2 .²⁵²⁰ They found an electron number of 3.5 at room temperature, at 60° and at 90°. Since the rate of some possible slow step in the reduction at room temperature would have been speeded up almost 100-fold at 90°, it was concluded that an equi-molar mixture of Tc (IV) and Tc (III) had been formed in the direct titration. They suggested that a dimer of technetium in the two oxidation states was the product of the reaction. With excess Sn (II), the technetium was entirely in the (III) state. Because all reactions were run under a nitrogen blanket, the stability of either of these species to air is not known.

Noll, Seifert and Muenze reacted K_4TcBr_6 with nitrilotriacetic acid (NTA) in dilute aqueous HBr.¹⁴⁰⁵ They obtained two different species after separation: a red solid, which they described as $\text{K}_2[\text{Tc}(\text{NTA})_2] \cdot 2\text{H}_2\text{O}$, and a brown compound, which they believed was $\text{K}_3\text{H}_4[\text{Tc}_2\text{O}_7(\text{OH})_4(\text{NTA})_2]$. Since both compounds were diamagnetic it was concluded that each was at least dimeric in technetium. The red compound which had IR bands at 715 and 553 cm^{-1} , was described as a binuclear oxygen-bridged Tc compound. The direct reduction by SnCl_2 of pertechnetate in a solution of NTA was characterized by a rapid consumption of 1.5 moles of Sn (II) per mole of technetium, formation of the red compound, and a slower reduction step consuming an additional 0.5 mole of Sn (II) per mole of technetium, presumably yielding a Tc (III) compound. This was readily air-oxidized to a red compound, which had the same visible absorption spectrum as the original product (bands at 500 nm and at 592 nm). Analysis by direct oxidation with a ceric salt was not informative, since the carboxylic acid groups were oxidized along with the technetium.

The same group carried out a more detailed and comprehensive investigation of the reactions of aqueous K_4TcBr_6 with monoamino- and polyaminopolycarboxylic acids, together with the reactions of the same ligands in the presence of pertechnetate which was reduced by SnCl_2 .¹⁴⁰⁶ They found a large number of both colored and colorless complexes of EDTA, NTA and DTPA with reduced technetium. Yellow, brown, red and purple species were formed with either K_4TcBr_6 or in the reduction system. The products were affected by pH, reagent concentration, etc. In the range of pH 2 all Tc complexes with DTPA, EDTA, HEDTA, NTA, IDA and EHIDA were anionic, and the mobilities increased with increasing pH. No Tc (V) complexes were formed in their experiments, unlike the results reported elsewhere.^{12419, 6077} They did not observe any stable colored Tc (III) species.

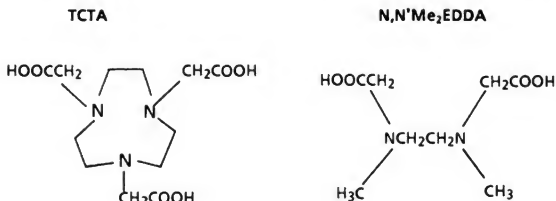


Blauenstein et al reduced pertechnetate with various reductants (SnCl_2 , tin metal and SO_2) in the presence of a number of aminocarboxylic acid ligands in water.^{408f} The ligands included NTA, EDTA, DTPA and IDA. During the reduction of pertechnetate in EDTA solution a colorless intermediate was formed which they believed to be a Tc (IV) complex. Technetium in solutions of the other ligands appeared to go directly to the final complex, which they thought was a Tc (IV) compound in each case, including EDTA. In a later paper Burgi et al prepared a crystalline Tc-EDTA complex, following reduction of pertechnetate with SO_2 .^{409f} Analysis of the red-brown crystals pointed to a mono-hydrate $[\text{Tc}(\text{H}_2\text{EDTA}(\text{O}))_2] \cdot 9\text{H}_2\text{O}$, but the structural analysis suggested a pentahydrate. The oxidation state of the technetium was difficult to determine. It could have been Tc (III) with u-OH groups, or Tc (IV) with u-oxo groups. The authors preferred the (IV) formula. The compound was diamagnetic, and the Tc-Tc distances were small enough to suggest metal to metal bonding. A related group reported the crystal structure of $\text{Na}_2[(\text{NTA})\text{Tc}(\text{u-O})_2(\text{Tc}(\text{NTA}))] \cdot 6\text{H}_2\text{O}$ whose composition resembles that of the EDTA complex.^{410f} Again there was some uncertainty about the oxidation state of the technetium. Two crystalline NTA complexes were isolated—one from low pH solutions and the other from neutral or slightly alkaline solutions. Both were diamagnetic.

Packard et al isolated a green solid from reacting $(\text{NH}_4)_2\text{TcCl}_6$ with $\text{Na}_2\text{H}_2\text{EDTA}$ in methanol.^{411f} The solid, which was not too soluble in water, was analyzed and appeared to be $(\text{Tc}(\text{OH})_2(\text{H}_2\text{EDTA})) \cdot 2\text{H}_2\text{O}$. In water the green compounds turned yellow and then red. The red product formed a calcium salt with the composition $\text{Ca}_2[\text{Tc}_2(\text{O})_2(\text{EDTA})_2] \cdot 4\text{H}_2\text{O}$. From its IR spectrum it appeared to be a dioxo-bridged technetium compound.

A large part of the complexities which are evident in this class of compounds was cleared up by the recent work of Linder on various aminocarboxylate complexes of technetium.^{344f} The complexities arise from two factors: the presence of dimers with the technetium in one or both of two oxidation states, and the formation of hydrolyzed dimeric species. $(\text{NH}_4)_2\text{TcCl}_6$ in an alcohol medium was reacted with Na_2EDTA under nitrogen, and a yellow-green solid was isolated. This was $(\text{HEDTA})\text{Tc}(\text{O})\text{Tc}(\text{HEDTA})$, which had the same structure, analysis, and physical properties as the yellow-green compound prepared by the reaction of SO_2 reduced HTcO_4 in the presence of Na_2EDTA and then oxidized. This green compound in turn hydrolyzed (in dilute EDTA solution) to form $(\text{H}_2\text{EDTA})\text{Tc}(\text{u-O})_2\text{Tc}(\text{H}_2\text{EDTA})$. The color changed from green to brown to muddy pink, and the absorption spectrum maxima shifted from 362 nm ($\epsilon = 3.5 \times 10^4 \text{ M}^{-1}\text{cm}^{-1}$) and 622 nm ($\epsilon = 450 \text{ M}^{-1}\text{cm}^{-1}$) to 502 nm

($\epsilon = 4200 \text{ M}^{-1}\text{cm}^{-1}$). Thus the technetium in some of the previous reports is a Tc (IV, IV) dimer. Linder found further that the reduction of pertechnetate by SO_2 in the presence of EDTA is complicated. A gold-colored solution is formed, which is then oxidized. If this is done rapidly with H_2O_2 in acid, the green mono-oxo compound is obtained. If it is done slowly, the muddy pink hydrolysis product is formed. A new ligand-1,4,7 triazacyclononane-N,N,N' triacetate (symbol TCTA), -N,N'



dimethylethylenediamine-N,N'-diacetic acid (N,N'Me₂EDDA) and NTA were used to prepare technetium bis (u-oxo) dimers for study. Their general formula was $[(\text{N O}_4)_x] \text{ Tc}(\text{u-O})_2 \text{ Tc}(\text{N O}_4)_x]^{4-}$ ($x = 1$ to 3). They were prepared by the reduction of pertechnetate by NaHSO_3 in aqueous solutions of the ligands, or by the reduction of the Tc (V) complex $[\text{TcO}(\text{EDTA})]_2$, which in turn was prepared from a quaternary ammonium salt of the TcOCl_4^- anion and EDTA in an organic solvent. In the bisulfite reduction the gold compounds appeared first. It was believed that they are Tc (III,III) dimers, but they have not yet been characterized. They form the Tc (IV,IV) dimers on oxidation. The TCTA complex could not be synthesized in this way. Instead it was made by oxidation from Tc(III,IV) dimer which in turn had been prepared by the reduction of a Tc (V) mixed complex of ethylene glycol and TCTA.

The new Tc (IV,IV) dimers resemble each other, and all show strong absorption bands in the 500-520 nm interval, and weaker ones near 600 nm. They are all diamagnetic. In the pH interval 1-4 they showed reduction in 1-electron steps by polarography. The NTA dimer, $\text{Na}_4[(\text{NTA})\text{Tc}(\text{u-O})_2 \text{ Tc}(\text{NTA})]$ reacted with NaOH above pH 10 to form a purple complex, listed by Noll et al.⁴⁰³ among other colored species found by them. On closer examination, when the NTA complex was dissolved in water and the pH was adjusted above 8 it reacted slowly, taking up 2 moles of base, and the product appeared to contain 2 moles of hydroxyl per mole of technetium. The change was readily reversed by acid. A barium salt of the basic form was isolated: $\text{Ba}_2[(\text{NTA}(\text{OH})\text{Tc}(\text{u-O})_2 \text{ Tc}(\text{OH}(\text{NTA}))]$. The Raman spectrum showed a Tc-O-Tc stretch and a Tc-O stretch, suggesting that a TcO_2Tc ring was maintained. In strong base (up to M NaOH) a deep blue product was formed by all the Tc (III,IV) dimers. The chemistry of these systems is obviously complicated, and has not yet been completely worked out. "It would appear that the formation of bis (u-oxo) dimers of Tc (IV) is a dominant theme in technetium aminocarboxylate chemistry."³⁴⁴ The (hydrolyzed) pink forms show peaks at or near 500 nm, and the Raman spectra show TcO_2Tc bridges. On reduction with hydrazine they undergo a reversible 1-electron reduction, to give deep blue dimers (probably Tc (III,IV)). On further reduction they may go to the gold compounds; this is not yet clear.

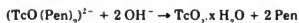
D. Thiol Complexes of Tc (IV)

1. Cysteine

The chemistry of thiol and dithiol complexes of Tc (IV) is in a poorly defined state, in contrast to the well-characterized chemistry of Tc (V)-dithiolates and mixed S-O or S-N complexes. Johannsen et al prepared various technetium complexes containing cysteine and cysteine derivatives.⁴¹² The preceding chapter described yellow Tc (V) thiol and dithiol complexes. In the present work, more extensive reduction of pertechnetate by excess cysteine or the displacement of bromide ions from TcBr_6^{2-} by cysteine (in water) gave red and green complexes which were purified by Sephadex gel chromatography. The absorption band maximum of the red material was at 540 nm ($\epsilon = 260 \text{ M}^{-1}\text{cm}^{-1}$) and that of the green complex was at 620 nm ($\epsilon = 480 \text{ M}^{-1}\text{cm}^{-1}$). There was also a fraction which emerged in the void volume of the column, and hence was probably polymeric or colloidal. The various cysteine derivatives yielded only green products. On electrophoresis the green cysteine complex (believed to be a Tc (III) compound) was negatively charged down to pH 2, and changed charge in more acid solutions.

2. Penicillamine

Penicillamine complexes of technetium were investigated by Yokoyama and Horiuchi.^{413, 267} They studied the effects of pH, of SnCl_4 , and of pertechnetate concentrations on the properties of the products. In addition to polymers and TcO_2 , they found two principal products. When the SnCl_4 concentration was only slightly in excess relative to pertechnetate (1.71) at pH 5-6, they found a yellow compound (absorbance maximum at 420nm, $\epsilon = 4600 \text{ M}^{-1}\text{cm}^{-1}$). Virtually the same spectrum was obtained when a TcCl_6^{2-} salt was reacted with penicillamine in water. It was therefore concluded that a monomeric Tc (IV) complex had been formed in each case, with this probable composition: $(\text{TcO}(\text{pen})_2)^{2-}$ where pen refers to the di-anion of penicillamine). At pH 1.5 with a larger excess of SnCl_4 (Sn-Tc ratio > 31) a complex was formed with a band maximum at 485 nm ($\epsilon = 6,000 \text{ M}^{-1}\text{cm}^{-1}$). On Sephadex gel filtration this complex was eluted before the yellow compound. It was therefore assumed to have a higher molecular weight, with the following structure: $\text{PenTcO}(\text{O}_2)\text{TcO Pen}$. The same product was formed when the reaction product of TcCl_6^{2-} and penicillamine was treated with SnCl_4 at pH 0.5. The effect of the added SnCl_4 was believed to be participation in the hydrolysis of Tc (IV).



An equilibrium constant for the decomposition of the complex was set forth which in an earlier publication had been evaluated in terms of the formation constant of the complex and the hydrolysis constant of the TcO^{2+} cation.⁴¹⁴ However, since the latter constant was based on the work of Gorski and Koch,³⁷⁶ which was not duplicated by other laboratories, it was decided not to examine those calculations further. In the reported kinetics of formation of the dimer, the following equation was used.

$$\frac{d(\text{D complex})}{dt} = k[\text{Tc}^2(\text{Pen})^2]$$

However, this does not prove that the complex is a dimer. The probability of a four-body collision is extremely small, and the products were not identified.

There is a possible different explanation for the chemistry of the technetium-penicillamine system. If there was air oxidation of the product of reaction between TcCl_6^{2-} and the ligand, forming a yellow Tc(V) complex, and if the latter is fairly stable, then excess SnCl_4 would reduce this yellow compound to a Tc(IV) complex, rather than a dimer. This explanation is consistent with the fact that the spectrum of a penicillamine complex prepared by displacement of a TcOCl_4^- salt (i.e. a Tc(V) salt) is identical with that of the monomer complex mentioned above.²⁶⁶ Either the reported Tc(V) complex (from TcOCl_4^-) had been reduced to a Tc(IV) complex by excess penicillamine, or the reported Tc(IV) complex (from TcCl_6^{2-}) had been air-oxidized to the Tc(V) compound, or both Tc(V) and Tc(IV)

in penicillamine have identical electronic orbitals. In this connection, the yellow absorption band of the monomer complex has virtually the same absorption maximum and the same molar absorptivity coefficient as a Tc(V) cysteine complex.⁴²⁴ A personal oral communication to one of us maintained that the Tc(IV)-penicillamine complex is extremely susceptible to air-oxidation.⁴¹⁵

3. Dimercaptosuccinate (DMSA)

Complicated reactions have been reported for the dimercaptosuccinate (DMSA) complexes of Tc (IV). Ikeda et al found that an incomplete reduction of pertechnetate by SnCl_2 produced a yellow complex (Complex I) with an absorption maximum at 390 nm.^{416, 417} In alkaline solution the peak shifted to 420 nm (Complex III). Addition of excess SnCl_2 in acid produced a purple complex with the absorption maximum at 520 nm (complex II) which in alkali formed either TcO_4^- (pH7) or another complex whose peak absorption was at 450 nm (Complex IV). A radiometric titration of pertechnetate in DMSA solution with SnCl_2 showed an end-point consistent with the formation of Tc (IV) (Complex I). From this it was reasoned that Complex II was a Tc (III) Complex, since it was produced by the action of excess SnCl_2 . In passing, it was noted that Complex II was almost completely adsorbed by a Biogel P-2 column, whereas Complex I was successfully eluted with 0.01M DMSA at pH 2. Complex II is the only technetium complex to date which is almost entirely taken up by a Biogel (Polyacrylamide) column, and appears to resist elution by ligand solutions.

There was no consideration of the possibility that in solution with insufficient SnCl_2 an extremely stable Tc(V)-DMSA complex might form (stable here means stable against dissociation). This is one of many dithiol complexes of Tc(V) with 5-membered rings and a Tc=O apical bond which were prepared and examined by Johannsen et al.⁴¹⁸ and were described in the previous chapter. The Tc(V)-DMSA complex reported there absorbed strongly at 410 nm for the racemic (d,l) form, and at 418 nm for the meso form. It appears, however, that the $\text{DMSA-SnCl}_2\text{-TcO}_4^-$ system is more complicated. First, the absorption maximum of Complex I is at 390 nm, whereas the Tc (V) complex (not prepared with SnCl_2) has its maximum at 410 nm. Secondly, Vanlic-Razumenic et al.⁴¹⁹ studied the dimercapto-propanesulfonate complexes of technetium, which are similar to those of DMSA, and found that while reduction of pertechnetate by the ligand itself and the preparation of a Tc (V) complex by ligand exchange with Tc(V)-gluconate gave the same complex with the same absorption maximum (400nm; $\epsilon = 2900 \text{ M}^{-1}\text{cm}^{-1}$), the reduction of TcO_4^- by excess SnCl_2 ($\text{Sn}:\text{Tc} = 31$) gave a yellow product with a spectrum different from that of the other two preparations.

Johannsen et al prepared two technetium complexes of DMSA which were believed to contain Tc (IV)⁴²⁰. The material prepared by SnCl_2 reduction, yellow-violet in color, had two components, which were separated by gel chromatography on Sepharose 6B. A quickly eluted brown fraction showed a sharply rising light absorption below 340 nm. A later fraction, violet in color, had a high constant absorption from 380 nm to 510 nm. The major part of either component did not move on electrophoresis. A displacement reaction run with DMSA on a TcBr_4^{2-} salt in water produced a substance with a weak absorption near 500 nm, and a band near 320 nm. The electrophoretic mobility of this material was 70% of the pertechnetate value. It was believed to be a polymer.

Vanlic-Razumenic and Petrovic prepared DMSA complexes from a kit to which they had added both $^{99\text{m}}\text{TcO}_4^-$ and $^{99\text{m}}\text{TcO}_4^-$.⁴²¹ After reduction by SnCl_2 at pH 2.6, the mixture was chromatographed on a Sepharose 2B column. Two complexes were formed, as reported by Ikeda.^{416, 417} Complex II stayed at the origin on a TLC plate, and Complex I had R_f 0.28-0.33 (that of $\text{TcO}_4^- = 0.5$) in physiological saline. In the view of these workers, it is not possible to prepare complexes of Tc-DMSA which are free of Complex I (which, according to them, localizes in bone). For Complex II, after purification they found that its absorption maximum was near 412-425 nm. It was yellow, not purple as reported by Ikeda. It localizes in the kidney.

It is apparent that there is a good deal of disagreement among three groups who have investigated Tc (IV) complexes of DMSA or similar ligands:

	<u>Tc (IV) peak, nm</u>	<u>Tc (V) peak, nm</u>
Ikeda	390 (acid)	
Vanlic-Razumenic	412-425 (acid)	
Johannsen	380-510 (SnCl ₂)	410-420
	300-500 (TcBr ₆ ²⁻)	

It would appear that a mixture of products had been formed, and that the method of preparation, or variation in the same method of preparation influences the properties of the final products.

E. Thiosemicarbazone Complex of Tc (IV)

A complex of technetium was formed by the reduction of pertechnetate with stannous chloride in the presence of potassium kethoxal-bis-(thiosemicarbazone) (KTS).⁽⁴²²⁾ The complex was extracted into various organic solvents, suggesting strongly that it carried no charge. It had an absorption maximum at 450 nm, as did a solution in which a TcCl₆²⁻ salt had been reacted with the thiosemicarbazone. There appear to be a number of products formed.

F. Complexes with Phosphorus (V) Ligands

1. Inorganic Phosphorus Compounds

a. Phosphate Complexes

The electrolytic reduction of pertechnetate in 0.1M phosphate buffered at pH 7⁽⁴²³⁾ or pH 4⁽⁴²⁴⁾ produced a pink complex. This had the same absorption spectrum as that recorded by a later group, who added exactly 1.5 moles of SnCl₂ for each mole of pertechnetate in 1M phosphate at pH 7 (max = 520 nm, $\epsilon = 2500 \text{ M}^{-1} \text{ cm}^{-1}$).⁽⁴²⁵⁾ Thomason⁽⁴²³⁾ also found that a more negative potential applied to the pink complex produced a Tc (III) green compound. Steigman et al⁽⁴²⁶⁾ duplicated this, and found, as Thomason did, that the green complex prepared at -0.85 volts versus standard calomel had absorption peaks at 610 and 738 nm, each with a molar absorptivity of about $300 \text{ M}^{-1} \text{ cm}^{-1}$. The Tc (III) complex was readily air-oxidized to the pink compound and required 1.0 electrons for re-reduction to the Tc (III) green complex. However, the species produced when an excess of SnCl₂ reacted with pertechnetate in 1M phosphate at pH 7 resembled neither the pink Tc (IV) nor the green Tc (III). It had a single peak at 738-740 nm with an absorptivity coefficient less than $200 \text{ M}^{-1} \text{ cm}^{-1}$. It was established that it was a mixed-metal complex containing Tc (III), Tc (IV) and Sn (II) in undetermined proportions.

b. Pyrophosphate Complexes

The reduction of pertechnetate by excess SnCl₂ in 0.2M sodium pyrophosphate solution at pH 7 could not be analyzed for unreacted Sn (II) by polarography,^(425b) because the Sn (II) oxidation wave at -0.24 volts versus the standard calomel electrode was severely distorted in the presence of

pertechnetate. At the same time, iodometric titrations were found to be unreliable in this system.⁽⁴²⁵⁾ Coulometry at fixed potential produced a pink color, which was followed by a pale blue. The pink compound was a Tc (IV) complex ($n=3$, $\lambda_{\text{max}}=520 \text{ nm}$, $\epsilon=500 \text{ M}^{-1} \text{ cm}^{-1}$). The coulometrically produced pale blue solution initially had Tc (III) ($n=4$) and was unstable, slowly liberating a gas (probably hydrogen) and reforming the pink complex. Excess SnCl_2 added to pertechnetate in 0.2M sodium pyrophosphate at pH 7 produced a faint blue color which deepened on standing. The final (limiting) spectrum, after 100 hours at room temperature, was the same as that of the coulometrically produced product after re-reduction. This was interpreted as the absence of any mixed-metal complex of tin and technetium. The kinetics of the formation of the blue compounds in the presence of excess SnCl_2 were second order in technetium concentration. The velocity constant was $490 \pm 74 \text{ LM}^{-1} \text{ h}^{-1}$ at room temperature. The reaction was probably a slow dimerization reaction. In a more concentrated pyrophosphate solution (1M $\text{K}_2\text{P}_2\text{O}_7$ at pH7), the coulometrically reduced technetium, yellowish in color, had an average electron number of 4.6 (a mixture of Tc (III) and Tc (II)). The product prepared with excess SnCl_2 in that medium was colorless, with no detectable light absorption in either the visible or near UV region. Dilution of this latter solution to 0.2M pyrophosphate produced no visual change in the colorless solution, even after the admission of air.

The Tc (IV) phosphate complex in solution has an absorption spectrum which closely resembles that of the Tc (IV) pyro-phosphate. This is also true of the Tc (III) phosphate and pyrophosphate spectra. These close resemblances may be due to complexation with a hydrogen-bonded phosphate dimer ligand.^(426, 427) The actual composition of any one of these technetium complexes is not known at present. It would appear, however, that there may be twice as many phosphate as pyrophosphate ligands in complexes of a given technetium oxidation state. Russell and Cash carried out amperometric titrations of approximately 10^{-4} M pertechnetate with SnCl_2 in a number of solutions, including 0.1M pyrophosphate at pH 7.⁽⁴²⁸⁾ They found an end point in the latter case which corresponded to the formation of Tc (IV). This same end point was found at -1.2V versus standard calomel on the TCO_2^- plateau, and at 0.2V on the Sn (II) oxidation plateau. This contradicts the previously cited paper in which the polarographic analysis of Sn (II) in pyrophosphate was abandoned because of interference from the reduced technetium.⁽⁴²⁹⁾ Russell and Cash found reduction from Tc (VII) to Tc (IV) in one step in the pH interval 3.0 to 12.0. They did not find Tc (III), although in their titrations they used up to 8 equivalents of SnCl_2 per equivalent of pertechnetate. In addition they did not notice the formation of a blue color which deepened in time.⁽⁴²⁹⁾ This is an additional point of disagreement with the previously cited research which remains to be resolved.

c. Tripolyphosphate Complex

The reduction of pertechnetate in tripolyphosphate solution ($\text{Na}_3\text{P}_3\text{O}_{10}$) was studied by Terry and Zeitel.⁽⁴³⁰⁾ They found that the electrolytic reduction of pertechnetate at pH 4.7 yielded a Tc(III) complex, which could be reversibly oxidized electro-chemically to a Tc (IV) complex. They developed a method of analysis of pertechnetate based on a controlled-potential coulometric reduction.

A more detailed investigation by Miller et al was carried out in order to characterize the coulometrically formed Tc (IV) and Tc (III) tripolyphosphate complexes.⁽⁴³¹⁾ The reduction of pertechnetate at pH 4.7 and at -0.75V (vs SCE) in 0.1M tripolyphosphate solution involved a 4-electron change, and hence generated Tc (III). The Tc (III) tripolyphosphate complex is readily oxidized to a Tc (IV) complex either by water or by air or by controlled potential electrolysis at -0.40 V (vs. SCE). Both complexes are yellow in the acid solution. The Tc (IV) complex has absorption bands near 570 nm and at 395 nm, and has an intense charge-transfer band below 350 nm. This Tc (IV) complex, initially prepared in acid, undergoes a rapid irreversible hydrolysis in alkali and a much slower acid-catalyzed hydrolysis. On reduction in alkali a Tc (III) complex is formed which has a different absorption spectrum from the Tc (III) species formed at pH 4.5. The Tc (IV) species formed at pH 4.5 by electroreduction to Tc (III) and reoxidation also hydrolyses, but at a very much slower rate. The electroreduction of the Tc (IV) alkaline complex is irreversible, and the Tc (III) complex so produced is different not only in absorption spectrum, but in polarographic characteristics from the Tc (III) species

produced in acid. The basic form has a small band near 700 nm, whereas the acidic product has a larger band near 700 nm, and another near 550 nm.

2. Organic Phosphorus Compounds

These complexes have been included under the Tc (IV) heading, although there is reason to believe that other oxidation states of technetium are also involved. In addition, the studies reported here include some reference to ^{99m}Tc chemistry. A separation of the discussions would have been artificial. The chemistry described here is limited to solution studies (with several exceptions) and consists largely of chromatographic separations.

a. Methylene Diphosphonate

Methylene diphosphonic acid was reacted with $(\text{NH}_4)_2\text{TcBr}_6$ in hot N,N -dimethylformamide.⁴³² After dilution with an aqueous acidic buffer, the brown product was adsorbed on an anion-exchange resin and eluted with LiClO_4 solution. Brown crystals were obtained from the eluate, with the composition $(\text{Li}(\text{H}_2\text{O})_3(\text{Tc}(\text{IV})(\text{OH})(\text{MDP}) \cdot 1/3 \text{H}_2\text{O})$ if one accepts the displacement reaction as predominant, with no subsequent oxidation. On the other hand, oxidation would lead to the composition $(\text{Li}(\text{H}_2\text{O})_3(\text{Tc}(\text{V})(\text{O})(\text{MDP}) \cdot 1/3 \text{H}_2\text{O})$. The X-ray diffraction data do not permit these and perhaps other compositional possibilities to be distinguished from one another. The technetium is 6-coordinate (octahedral). The solid consists of infinite polymeric chains. Methylene diphosphonate can bridge two technetium atoms, and each technetium is bound to two MDP ligands. The oxidation state of technetium in MDP solutions containing pertechnetate was determined by polarographic measurements, and appeared to be (IV) in acid, neutral and alkaline solutions.⁴³⁸ This does not preclude the formation of the other technetium oxidation states by chemical reducing agents in MDP solution.

HPLC was used to characterize both carrier-added and no-carrier-added technetium-MDP formulations.⁴³³ The purpose of this investigation was the examination of the bone-imaging properties of various separated fractions. The Tc-MDP complexes were prepared by the reduction of pertechnetate by NaBH_4 at pH 2,6,8,9,10 and 12. Both aerobic and anaerobic solutions were studied. On the acid side both types gave yellow solutions. At pH 8 the anaerobic solution was green, and the aerobic solution turned yellow on standing. At pH 9 the anaerobic specimen was greenish-blue, and the aerobic specimen slowly turned orange-red. At pH 10 both turned pink on standing. At pH 12 both were colorless. These obviously complicated changes, which were both time- and pH- dependent appear to have little connection with the brown compound obtained by displacement.⁴³⁷ The HPLC separations were conducted on an anion-exchange column with 0.85M sodium acetate as the eluant. Depending on the pH, 2 to 5 peaks were observed (more in alkali than in acid). With the carrier-added solution there was visible but limited interconversion by changing pH. The no-carrier-added samples showed two peaks in acid and four in alkali, and much more interconvertibility of peaks by changing pH than the other specimens. The conclusion was drawn that "increasing the formulation pH favors production of complexes with short retention times, which within the modes of anion exchange chromatography corresponds to complexes of low negative charge density."⁴³³ This appears to mean that a higher charge density in a complex anion means a longer retention time - or a greater selectivity coefficient - with respect to anion-exchange columns. The conclusion is incorrect; if anything, the reverse is true. This question will be discussed at some length in the Tc-HEDP section below.

It was noted that the no-carrier-added solutions (10mCi of ^{99m}Tc) had an initial concentration of $7 \times 10^{-9}\text{M}$ in ^{99m}Tc . Unfortunately, the total TcO_4^- concentration ($^{99}\text{Tc} + ^{99m}\text{Tc}$) in the samples was not determined. The probability of oligomeric complex formation rests at least in part on the kinetics of reaction of these very dilute systems, and hence on the absolute concentration of total technetium.

b. Hydroxyethylidene Diphosphonate

1. Oxidation State of Technetium

The oxidation state of technetium which had been reduced from TcO_4^- by excess SnCl_2 in 0.2M Na_2EHDP at pH 5 was determined by a polarographic analysis of unreacted Sn(II) .⁴²⁵ Two maxima were observed, one at -0.12V and the other at +0.080V (versus standard calomel). The concentrations of tin were equivalent to a 4-electron and a 3-electron change respectively. The waves were poorly defined.

Russell and Cash performed fast pulse polarography on pertechnetate in acid, neutral and alkaline solutions of EHDP.⁴²⁸ They reported the formation of Tc (III) in the acid solution, and the formation of Tc (V) in neutral and alkaline solution.

A fast-scan cyclic voltammetric study of the reduction of pertechnetate in EHDP at pH 3.5 and 7 gave somewhat different results.⁴³⁴ There was an initial reversible 1-electron reduction, followed by the formation of Tc (V) in a complicated fashion. This product may have undergone further reaction with ligand or solvent molecules. There was an additional reduction step in a second reduction peak. It was hypothesized that this step (at pH 7) formed Tc(IV). The time scale for this operation was in milliseconds. The usual polarographic studies require seconds, and slower reduction reactions following the rapid ones may well have been observed in the usual studies.

Amperometric titrations of pertechnetate in acid EHDP solution with SnCl_2 showed a three-electron change, forming Tc (IV).⁴³⁵ Excess SnCl_2 was back-titrated with I_2 , and gave the same result.⁴³⁶ This latter titration (without potentiometry) had been carried out by Hambright et al, who drew the same conclusion.⁴³⁷ However, this is not a definitive finding, since the same data would have been obtained if a lower oxidation state (like Tc (III)) had been oxidized to Tc (IV), along with a smaller titer of unreacted SnCl_2 .²⁹⁴ A specific analysis for unreacted SnCl_2 would have been preferable.

Muenze reacted a TcBr_6^{3-} salt with EHDP, and isolated a solid whose composition was $[\text{K}_2\text{TcO}(\text{OH})]^{3+} [\text{EHDP}]^{3-}$.⁴³⁸ While this seems to establish that the product is a Tc (IV) complex of EHDP, its preparation by displacement in water rather than in a non-aqueous solvent raises the possibility of complications from the independently occurring hydrolysis of the TcBr_6^{3-} anion.

2. Number and Nature of Tc (EHDP) Complexes

Van den Brand et al examined reaction mixtures containing pertechnetate, SnCl_2 and EHDP at pH 7 in water by gel chromatography.⁴³⁹ They used the cross-linked polyacrylamide gel Bio-Gel P-4 rather than Sephadex because of the possibility that Sephadex would decompose Tc-EHDP complexes.⁴³⁷ As it turned out, the complexes decomposed on Bio-Gel. It was necessary to add Na_2EHDP to the saline eluant in order to avoid this decomposition. They assumed that the gel functioned by steric exclusion and, accordingly, they calibrated the column with a variety of inorganic and organic compounds of different molecular weights preliminary to the estimation of the molecular weights of any Tc-EHDP complexes. Technetium-99 was run at 10^{-4}M , and Technetium-99m at 10^{-11} - 10^{-12}M . The technetium elution curves were unsymmetrical in shape, suggesting that a number of compounds were being eluted close to one another. The curves were analyzed by an iterative procedure, on the assumption that they were made up of closely lying Gaussian curves. By this procedure they found 5 components with ^{99}Tc , and four of the five with ^{99m}Tc . ^{113}Sn was found with two components, was possibly present in a third, and was absent in any other. The P-Tc ratio was determined with ^{32}P -labeled EHDP. Since four of the five fractions assigned to Tc-99 were found with ^{99m}Tc fractions, they reasoned that all five must be monomeric in technetium, because of the

improbability of dimer formation in a reasonable period of time in solution with 10^{-11} - 10^{-12} M technetium. This led to the conclusion that any molecular weight greater than that of Tc-EHDP was due to the incorporation of tin, to more than one EHDP per technetium, to tin plus an additional EHDP, or to three molecules of EHDP per technetium atom. On this basis the compounds were eluted in the order: Tc (IV)-EHDP, Tc (IV)-Sn (IV)-EHDP, Tc (IV)-(EHDP)₂, Tc (IV)-Sn (IV) - (EHDP)₂ and Tc (IV)-Sn (IV)-EHDP₃.

3. Theory of Determining Charge to Mass Ratio

These conclusions concerning the chemical form of the Tc EHDP complexes are open to question for reasons which are set forth below

4. Theory of Gel Chromatography

In gel chromatography there is a sieving or steric exclusion effect. Smaller molecules will diffuse into gel pores which are too small to admit larger molecules, and hence will take longer to be eluted. The following equation describes the behavior of solutes:⁴⁴⁰⁾

$$V_i = \frac{(W - W_t - a - \rho V_o)}{\rho}$$

W is the total column weight, W_t the column tare weight, a is the dry gel weight, ρ is the density of water at the operating temperature, V_o is the void volume, and V_i is the volume of solvent in the interior of the gel beads. There is a distribution coefficient, K_n, for any particular solute:

$$K_D = \frac{V_e - V_o}{V_i}$$

Here V_e represents the volume eluted with a particular solute. This equation is exact, but represents more work than various alternative convenient forms which may require simpler measurements. One example is in which V_s is the elution volume of some uncomplicated substance:

$$K_D = \frac{V_e - V_o}{V_s - V_o}$$

tritiated water has been used frequently for this purpose with aqueous eluants. V_o, the void volume, is usually determined with a totally excluded high-molecular-weight substance like Blue Dextran. K_D represents the fraction of imbibed volume which is available for gel penetration. Values of K_D may vary between zero and unity. A value of zero represents complete exclusion from the interior of the gel. A value of unity represents complete penetration, indistinguishable from the behavior of, let us say, tritiated water. If K_D exceeds unity, then adsorption by the gel is clearly indicated, and the solute is not subject to simple steric exclusion. Indeed, Gelotte, who did early research on gel chromatography, considered that a value of 0.8 or more indicated solute adsorption.⁴⁴¹⁾

The equation used by Van den Brand et al was:

$$K_d^1 = \frac{(V_s - V_{BD})}{(V_{Na} - V_{BD})}$$

in which V_s is the volume of the solute eluant, V_{BD} is the Blue Dextran (BD) void volume, and V_{Na} is the elution volume of labeled Na (^{22}Na) in the sodium chloride eluant.

There is an implicit assumption that NaCl has a K_d^1 (or K_D) of unity in BioGel P-4. However, this is not the case, and that changes the interpretation of their results. Saunders and Pecsok⁴⁴⁰ investigated the elution of aqueous solutions of 62 inorganic compounds from Bio-Gel P-2 (which is somewhat more highly cross-linked than P-4). They concluded that all of them were eluted by an adsorption-desorption mechanism rather than by steric exclusion. Their eluant was distilled water. In this connection, both Sephadex and Bio-Gel resins are known to have small concentrations of fixed anionic charges—probably carboxylate groups—which will introduce a Donnan effect. Usually this is minimized or eliminated by elution with an electrolyte solution, e.g., 0.1M NaCl. However, Saunders and Pecsok were able to use distilled water as the eluant because they found that while Sephadex G-10 samples had 2 micro-equivalents per gram of unit negative charge, their batch of Bio-Gel had only 0.02 micro-equivalents of negative charge per gram, which was negligible. They reported that the K_D for NaCl was 1.27. Van den Brand et al had assumed in effect that it was unity. If we assume that Bio-Gel P-4 is not very different from Bio-Gel P-2, correct the V_{Na} term in their equation to reflect what water would have done, i.e., divide V_{Na} by 1.27, insert the values for Blue Dextran elution and recalculate, the equation would be:

$$K_D^1 = \frac{(V_s - V_{BD})}{(V_{Na} - V_{BD})} = \frac{(V_s - 45.0)}{\left(\frac{123.75}{1.27} - 45.0\right)} = \frac{(V_s - 45.0)}{(97.4 - 45.0)} = \frac{(V_s - 45.0)}{(52.4)}$$

This introduces the following changes in the K_D^1 values for their reference compounds: that for sodium phosphate increases to 1.22, that for sodium pyrophosphate becomes 1.01, the glycylalanine value becomes 1.08, and L-leucyl-L-tyrosine is increased to 1.23. In these recalculations it was assumed that each solute, including Blue Dextran, is unaffected by the behavior of the saline eluant.

5. Separation by Molecular Weight on Gel Chromatography

Beyond this particular argument, there is also evidence that no simple relationship exists between the molecular weights of some simple organic compounds and their elution volumes from Bio-Gel P-2. Politti et al reported that they found good separations of low-molecular-weight organic compounds by eluting them from Bio-Gel P-2, but that the separations did not depend on molecular weight.⁴⁴² They were unable to draw a calibration curve (log molecular weight versus elution volume) with P-2 at any linear flow rate for molecular weights ranging from 100 to 1800 daltons.

It can be concluded that Van den Brand et al found at least four different compounds containing ^{99m}Tc , but the molecular weights assigned by them are in doubt, as are their compositions. In this connection, work by Pinkerton et al (described below) used HPLC with an anion-exchange resin and a sodium acetate eluant on the products of reduction of pertechnetate in EHDP solution. With NaBH_4 as reductant they found 12-13 distinct peaks. With SnCl_2 as the reductant seven of 15 were the same as the products from NaBH_4 reduction. Of the peaks produced by SnCl_2 , only one—a distinctly minor peak—contained ^{113}Sn . This suggests that Van den Brand and his collaborators did not have enough

resolving power in their low-pressure chromatographic column to separate tin-bearing peaks from closely lying technetium-containing peaks. There is another disagreement between the two researchers; Pinkerton et al reported that if the total technetium present was less than 10^{-7} M, most of the peaks vanished, and one predominant (mononuclear) species remained.⁴⁴³ This is in marked contradiction to the Van den Brand finding that four fractions containing technetium were found in the ^{99m}Tc solutions whose technetium concentrations were 3 to 4 orders of magnitude less than 10^{-7} M.

In retrospect, Sephadex would have been a more suitable column material than Bio-Gel. The use of the polyacrylamide, after all, still required the addition of the sodium salt of EHDP to the eluting solution in order to prevent adsorption of the complexes to the column. A similar addition to the NaCl eluant for Sephadex would probably have been successful, since gluconate and pyrophosphate complexes of technetium are stabilized against adsorption to Sephadex by the addition of gluconate and pyrophosphate salts, respectively, to the eluant. The reason for preferring Sephadex to Bio-Gel is that steric exclusion is the mechanism of separation of many compounds, including some inorganic compounds on Sephadex columns. The one difficulty is the Donnan effect mentioned earlier, and this is practically eliminated by elution with an indifferent electrolyte. In this connection, for reasons which are not now known, NaTcO_4 is strongly adsorbed on both Sephadex and Bio-Gel resins. This is why it is eluted well after various reduced technetium complexes in analytical gel-chromatography.

6. Separation by Ion Exchange

The application of HPLC techniques to the analysis of Tc-HEDP complexes was undertaken by Pinkerton, Heineman and Deutsch,⁴⁴⁴ using millimolar pertechnetate reduced by NaBH_4 and tagged with ^{99m}Tc . The column consisted of a strongly basic anion-exchange resin, Aminex A-27. The eluant was 0.85 M sodium acetate which was maintained at pH 8.4. The elutions were monitored by radiation detection and by UV scanning. A large number of components were found, including several which were produced only in the presence of air.

Pinkerton and his associates later continued this work. With the same sodium acetate eluant they found 13 fractions produced by NaBH_4 reduction.⁴⁴⁵ They also found that reduction by SnCl_2 produced at least 15 fractions (without exposure to air) and reported that seven of these were also among the fractions resulting from borohydride reduction.⁴⁴⁶ The identification of fractions common to the two reducing systems was based on UV spectra and on chromatographic retention times. It has already been noted that ^{113}Sn was found unambiguously in only one minor fraction of the 15, and this was true only up to pH 7. In alkaline solution no tin was detected in any technetium fraction. This work made possible the testing of a number of the separated fractions in radiopharmaceutical preparations^{447, 448} and is undoubtedly valuable in an applied sense. However, the same investigators attempted to deduce both the electrical charges and the molecular sizes of the various fractions almost entirely from the retention times of these fractions, and several serious questions must be raised about the theoretical basis underlying their treatment.⁴⁴⁹

There is no difficulty in relating the retention time to the selectivity coefficient of a particular anionic species:

$$\ln t_R = \ln \frac{V_s}{F} + \ln K_p$$

Here t_R is the corrected retention time of species i , V_s is the stationary -phase volume; F is the volume flow rate, and K_p is the distribution coefficient of species i , defined as the molar concentration of the species in the resin, $C_{i,r}$, to the molar concentration of the same species in the sodium acetate eluant, $C_{i,e}$. The equation assumes that there is virtual equilibrium at every stage in the elution, and hence elution patterns can be related to the ion-exchange behavior of the various anionic species in the Tc-HEDP mixture. If one knew the structures and other characteristics of all these species, one could

then relate them to the retention times, and then decide how such properties as size and partial molar volume contribute to the chromatographic behavior of each species. However, it is the reverse operation which is attempted here: to determine charges and volumes of the eluted species from the retention times. In order to do this, a model (incorrectly described as a rigorous thermodynamic treatment) was put together, based on the following factors:

1. The electrochemical potential of a technetium species in the external electrolyte solution is set equal to the standard chemical potential, the ion activity in the external electrolyte, and the product of the ionic charge and the electrical potential acting on the ion;
2. The electrochemical potential of the same species in the water phase is set equal to the same corresponding terms in the resin phase plus the osmotic pressure of the resin multiplied by the partial molar volume of the (solvated) species;
3. Similar expressions are generated for the eluant anion, acetate, and the assumption is made that the Donnan potential (the difference between the resin potential and the solution potential acting on the ion i) will be the same as that experienced by the acetate eluant. This eliminates these common terms by dividing through by the charge Z_i on the i ion and the charge Z_A on the acetate;
4. In the evaluation of partial molar volumes, the standard states are selected so that the activity coefficients are unity at infinite dilution. Hence the standard electrochemical potentials are the same in both resin and electrolyte phases for both the acetate and any technetium species under consideration;
5. The activity coefficients of acetate and of the complexes are averaged out on the basis that an ion spends time in both the resin phase, which has a high ionic strength (estimated at 3.5M) and in the 0.78M sodium acetate eluant;
6. The final working equation relates the retention time to the charge Z_i on a species i , multiplied by the acetate activity in the external solution:

$$\log t_{R_i} = \text{intercept} - Z_i \log A_{Aet}$$

The concentration of sodium acetate was varied over a small range - (0.740 to 0.815M), each fraction was studied over this range, the log of the retention times was plotted against the calculated log of the activity of the acetate ion (calculated from an expanded Debye-Huckel equation) and the resulting slope gave the charge, Z_i , on that anionic complex.

7. Separation by Charge on Ion Exchange Chromatography

It was assumed in this treatment that a species with a higher negative charge will be held longer on the anion-exchange resin column than a species with a smaller negative charge, because of electrostatic interactions. This is a major error in setting up equations relating the flow time to various factors, including charge. The inclusion of the term $z F \Phi$ in the basic equation (that is, the charge on a complex, the Faraday constant and the electrical potential acting on the ion i either in the external solution or in the resin phase) means that the authors were following an early statement by Helffrich that "the ion exchanger prefers the counter-ion of higher valence."⁴⁹ The Donnan potential is the cause of this particular interaction, which has been called "electroselectivity." However, this is not the same as the measured selectivity coefficient, and at best may be a contributing factor to the coefficients found in cation-exchange sulfonate-based resins. In these, the charge density of the solvated alkali cations seems to affect the order of selectivity coefficients: $Cs^+ > K^+ > Na^+ > Li^+$, and a more highly charged cation like Ca^{2+} is more strongly taken up than the less highly charged Na^+ .

There is additional evidence from the self-diffusion coefficients of cations in the resin phase, which are markedly affected by the charge on the ion. In Dowex-50X8 at 25°, an increase of one unit of positive charge on the cation decreases the coefficient about tenfold in the sequence $\text{Na}^{1+} \rightarrow \text{Th}^{4+}$.⁴⁵⁰ However, strongly basic anion-exchange resins behave differently. In self-diffusion studies in the resin phase, the effect of charge is quite small.⁴⁵⁰ In equilibrium studies they do not show any preference for more highly charged ions. On the contrary, their behavior is characterized by a decreasing selectivity with increasing anionic charge. However, the comparison of charge types must be made carefully. The sulfate anion in HPLC operations is known to be eluted after the halide ions from a Dionex anion-exchange column, in widely seen advertisements. This may have given rise to the conclusion that the divalent charge on the sulfate anion is mainly responsible for its stronger retention by the resin. There are many examples of the effect of anionic charge on resin selectivity of more closely related species:

- i. According to Aveston et al, the $\text{Au}(\text{CN})_2^-$ ion displaces other cyanide metal complexes from Amberlite IRA 400, the ease of displacement increasing with increasing negative charge. Thus, its selectivity coefficient against $\text{Ni}(\text{CN})_4^{2-}$ is 246, and that against $\text{Fe}(\text{CN})_6^{3-}$ is 6×10^9 .⁴⁵¹
- ii. In the text by Marcus and Kertes there are a number of examples of resin preference for an anionic complex of lower charge in spite of the existence in the aqueous solution of more highly charged complexes:⁴⁵²

AgCl_2^{3-} in solution, AgCl_3^{2-} on the resin;

$\text{Ag}(\text{S}_2\text{O}_3)^{3-}$ in solution, $\text{Ag}(\text{S}_2\text{O}_3)^{1-}$ on the resin;

$\text{Ag}(\text{CN})_4^{3-}$ in solution, $\text{Ag}(\text{CN})_3^{2-}$ on the resin;

$\text{La}(\text{S}_2\text{O}_3)_3^{3-}$ in solution, $\text{La}(\text{S}_2\text{O}_3)_2^{1-}$ on the resin;

$\text{Gd}(\text{HOCH}_2\text{COO})_6^{3-}$ in solution, $\text{Gd}(\text{HOCH}_2\text{COO})_4^{1-}$ on the resin

- iii. The selectivity coefficients for tracer anions with different charges were determined on Dowex-1X8.⁴⁵³ Against chloride ReO_4^- had a selectivity coefficient of 570, the CrO_4^{2-} coefficient was 0.18 and that of WO_4^{2-} was 0.07. Against cyanide $\text{Cr}(\text{CN})_6^{3-}$ had a coefficient of 2, and $\text{Fe}(\text{CN})_6^{4-}$ had 0.06. The authors concluded: "at least in these cases of (large) anions with a strong-base resin, electrostatic ion pairing in the resin phase is not important."
- iv. In the course of studying electron exchange between ferri- and ferrocyanide, Cobble and Adamson found that they could quickly separate ferricyanide from ferrocyanide by elution through a column of the anion-exchange resin Amberlite IR-4 in the carbonate form.⁴⁵⁴ The resin preferentially absorbed the less charged ferricyanide, and allowed the more highly charged ferrocyanide to be eluted.
- v. There is a large number of studies of the adsorption of sulfuric acid from aqueous solution by a strongly basic anion exchange resin in the sulfate form.⁴⁵⁵ This is called site-sharing, but it comes down to the idea that two bisulfate anions are held more strongly than one sulfate.
- vi. MnO_4^{2-} is more weakly taken up by a strongly basic anion exchange resin than MnO_4^- .⁴⁵⁶
- vii. Similar conclusions—that the more highly charged anion is less firmly held on a resin than the lesser charged species—have been drawn for the phosphate system⁴⁵⁷ and for the carbonate-bicarbonate system.⁴⁵⁸

These examples show that the electrostatic hypothesis used by Pinkerton et al does not hold for anion-exchange resins. Even for sulfonic acid cation-exchange resins the electrostatic effect is not very strong: perhaps a factor of 2 for the ions $\text{Na}^+ \rightarrow \text{Ca}^{2+}$.⁽⁴⁵³⁾ The process called ion exchange is more complicated than a simple exchange of ions of either charge type. This had led Helffrich to comment: "the mechanism of the separation may be as far removed from exchange of ions as chromatography is from color."^(459a)

8. Separation by Molecular Weight on Ion Exchange Chromatography

A second source of error about the properties of anion-exchange resins in the work under consideration concerns the size or molecular weight of the fraction separated on the Aminex resin. The comment is made that the elution order of three of the fractions (M, P and S) "of effectively equal charge can be seen with M eluting first, because of its greater partial molar volume. This demonstrates that the discrimination of partial molar volume is an integral part of ion-exchange theory."⁽⁴⁴⁵⁾ This is incorrect; experience teaches that the reverse order has been observed. Beukenkamp et al determined the exchange constants and the distribution ratios of phosphate and condensed phosphates against chloride on a strongly basic anion-exchange resin.^(459b, 459c) They found that the exchange constants and the distribution ratios for a given negative charge decreased in the order orthophosphate, pyrophosphate and triphosphate. That is, the larger the anion in this series, the greater is its attachment to the anion-exchange resin. In the same vein Iguchi reported that polythionates, all of which bear the same divalent charge, can be separated on an anion-exchange column, and the largest one is eluted last.^(459d) It will be recalled that the polythionate anions have the general formula $(\text{S}_n\text{O}_6)^{2-}$, and n has the values 2, 3, 4, 5.

9. Activity Coefficients for Ion Exchange Chromatography

A third source of error in the work under consideration is the calculation of the activity coefficients of the complexes in the resin phase and in the eluant. These calculations are based on the use of the expanded Debye-Huckel equation, treating the anion-exchange resin phase as if it were only a concentrated aqueous electrolyte solution whose effect on activity coefficients emerged only from its ionic strength. In order to see the error involved in this treatment, one must look at a rigorous thermodynamic treatment of ion-exchange resins.^(460, 461) The exact Gibbs-Donnan equation for ion-exchange equilibria in charged membranes with a hydrostatic pressure is:

$$RT \ln K_a = P(z_1 \bar{V}_1 - z_2 \bar{V}_2)$$

in which K_a is the activity product ratio for the exchange of ion 1 by ion 2, $\bar{V}_1$ and $\bar{V}_2$ are the partial molal volumes of the exchanger salts, P is the pressure, and z_1 and z_2 are the charges carried by the two ions. For the simple case of two singly charged ions, this becomes:

$$\log D_1^2 = \frac{P(\bar{V}_1 - \bar{V}_2)}{RT} + \log \left(\frac{\gamma_1}{\gamma_2} \right)_y - 2 \log \left(\frac{\gamma_1}{\gamma_2} \right)_w$$

Here D is the selectivity coefficient for ions 1 and 2 (this is not the square of D_1 , $(\gamma_1/\gamma_2)_y$ is the ratio of the activity coefficient of the two exchanger salts in the resin phase and $(\gamma_1/\gamma_2)_w$ is the ratio of the mean molal activity coefficients of the halide salts 1 and 2 (NOT the ions) in the water phase. The first two terms were evaluated accurately from weight swelling measurements conducted together with isopiestic vapor-pressure measurements on resins whose cross-linking with divinyl benzene varied from almost zero (0.5% DVB) to 24%. The third term in the equation was evaluated by means of data in papers in the literature which dealt with mixtures of electrolytes. It is not practical to go into

all the details of these very thorough researches. There are three points of immediate interest: 1) the authors were able to evaluate the three terms on the right-hand side of the equations, as well as the selectivity coefficients for the halide-ion exchanges. They found that the osmotic pressure term and the aqueous electrolyte activity coefficients (the first and third terms of the right-hand side of the equation) were of decidedly minor importance. The important term was the log of the ratio of the activity coefficients of the two resin salts in the resin phase. This was also true of cation-exchangers (for alkali-alkali or $\text{Na}^+ - \text{H}^+$ exchanges).¹⁴⁶⁰ 2) The reference state selection offered a severe problem. It was not possible to measure the water uptake on resin mixtures so dilute that the ratio of the two exchanging ion coefficients was unity (i.e., $\log(\gamma_i/\gamma_j)$, in the limit approached zero). Instead a very lightly cross-linked resin (0.5% DVB) was used for the reference state on the basis that the selectivity would practically vanish, since it is known to increase for any pair of ions with increasing cross-linking. This worked for a cation-exchanger.¹⁴⁶⁰ Thus, the selectivity coefficient for the $\text{Na}^+ - \text{H}^+$ exchange, which was 6.38 (at 25°) for a 24% cross-linked sulfonic acid resin, was unity for the 0.5% cross-linked resin. However, this was not true of the halide exchanges in the anion-exchange resins.⁴⁶¹ In all cases studied ($\text{Br}^- - \text{F}^-$, $\text{Br}^- - \text{I}^-$ etc.) the unexpected finding was that even for these weakly cross-linked resins, the selectivity coefficients were well above unity. For $\text{Br}^- - \text{Cl}^-$ it was about 2; for $\text{Br}^- - \text{I}^-$ it was above 4 and for $\text{Br}^- - \text{F}^-$ it was 10. This meant that the anions in these lightly cross-linked resins were (relatively) much more tightly bound than the alkali cations in the corresponding sulfonate resins. This is possibly associated with the properties of aqueous solution of quaternary ammonium salts. They show a marked difference of response to different anions as, for example in the mean activity coefficients, the effect increasing with increasing chain length. Thus, in 0.5 molal solution at 25°, the mean activity coefficient for the tetra-n-propylammonium halides are: 0.322 for the iodide, 0.486 for the bromide, 0.615 for the chloride, and 1.05 for the fluoride.⁴⁶² In contrast, for the potassium halides at the same molality, the coefficients are: 0.676 for the iodide, 0.657 for the bromide, 0.649 for the chloride, and 0.670 for the fluoride.⁴⁶³ If one takes the 3.5M estimate of ionic strength in the resin phase offered by Wilson and Pinkerton the disparity is very much greater. The quaternary ammonium iodide is too insoluble, but at 4 molal (which is less than 3.5M by virtue of water expansion) $\gamma_{\pm}$ for tetra-n-propylammonium bromide is 0.382, for the chloride it is 1.171, and for the fluoride it is 33.25.⁴⁶² Again, by way of contrast, in 4 molal solution at 25°, $\gamma_{\pm}$ for KI is 0.673, for bromide it is 0.600, for chloride it is 0.577 and for fluoride it is 0.779.⁴⁶³ While the corresponding effects for the benzyltrimethylammonium groups in the anion-exchange resins may be smaller than those associated with tetra-n-propylammonium salts, it is a mistake to treat the anion-exchange resin phase as no more than a concentrated aqueous electrolyte solution characterized mainly by its ionic strength.

A most important conclusion reached by Boyd and his collaborators is relevant here. Apart from possible specific effects, the selectivity coefficient for a pair of ions is a function only of the weight swelling (i.e. water uptake) of the resin. Anything that changes the swelling will change the selectivity in a manner that can be calculated from the Gibbs-Donnan equation. This includes factors like exchanger cross-linking, counter-ion composition, or external electrolyte concentration. Any decrease in the water content of an exchange resin by any means will increase a given selectivity coefficient. The authors point out that an increase in pressure applied to a weakly cross-linked resin could make it behave like a more highly cross-linked resin (at a lower pressure). That is, the selectivity coefficient of a pair of anions could be increased in this way.

10. Theoretical Considerations

The discussion up to this point has relied largely on experimental findings. There is an underlying qualitative concept which may be useful. This is the effect which various electrolytes are believed to have on the structure of liquid water, and the interactions which result from these effects. Simple inorganic salts fall into two limiting categories: water structure-formers and structure breakers.^{484, 485} The structure-formers are small or highly charged ions of high charge density which can force a structure of a number of layers of the surrounding water molecules so that the water dipoles are all oriented towards the central charge. Ions like lithium, calcium, fluoride and sulfate are structure-formers. Structure-breakers are larger ions like cesium, bromide, iodide and perchlorate which do not have a large enough field to force re-orientation of water dipoles in surrounding layers, but will nevertheless disrupt the water structure immediately adjacent to them. Viscosity measurements, among other techniques, demonstrate both effects. The structure-formers increase the viscosity of water, an effect which increases with increasing concentration. On the other hand, a moderately concentrated solution of cesium bromide, a structure-breaker, has a viscosity which is less than that of water itself at room temperature.⁴⁸⁴ There is a third group of salts-organic electrolytes, and in particular quaternary ammonium salts. It is thought that these salts organize the water molecules around themselves in an expanded hydrogen-bonded network which is similar to that of liquid water, rather than the compacted, denser ion-dipole-based structure formed by ions like lithium and similar inorganic structure formers. The effect of the organic cations on the water structure increases with increasing paraffin chain-length, and it varies considerably with different counter-ions. With respect to anion-exchange resins, the anions which are most strongly taken up are structure-breakers like iodide, perchlorate, perhenate and pertechnetate, as well as various anionic metal complexes - halide and cyanide complexes, for example. Those which are most weakly held are structure-formers like fluoride, hydroxyl, acetate, and anions with higher charges. Water accompanies such anions into the resin phase. The water uptake by the resins is least for those anions which are strongly taken up and is greatest for anions which are weakly held.⁴⁸⁶ Whitney and Diamond have discussed the water distribution in anion-exchange resins and the competition between water solvation of anions and resin uptake.⁴⁵³ They pointed out that both the osmotic pressure-volume and electrostatic ion-pairing models fail to explain anion selectivity, and projected water-structure-enforced ion pairing as the explanation.^{472a} That is, the introduction of large (especially large and hydrophobic) ions into water forces a minimization of the volume occupied by such anions and will thus force them into intimate contact with the quaternary ammonium ions in the resin, which are also large and not hydrated. They pointed out that such ion pairing, which is not electrostatic, is seen primarily with monovalent anions, and is more important the larger and more hydrophobic the anion. This may be the explanation for the increase in selectivity coefficients with increasing anionic size noted earlier for the various polyphosphates^{459b, 459c} and the polythionates.^{459a} This and the preceding explanation focus on changes in the water as the driving force for anion-exchange selectivity.

G. Tc(IV) Phosphines and Related Complexes

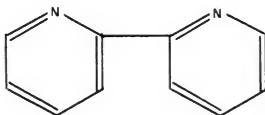
Trialkyl, triaryl and mixed phosphines and arsines readily form complexes with transition metals. They behave like Lewis bases; they donate electrons to the metal ion, forming sigma bonds- but they also accept back-donated electrons in their lower empty pi orbitals. The back-donation means that lower oxidation states of metals are favored in this type of complex formation because there are more electrons in those states which can interact with the empty pi orbitals of the ligand. The phosphines and arsines are also effective reducing agents.

The first Tc(IV) phosphine complexes were prepared by Fergusson and Hickford by reacting $TcCl_4$ in ethanol with triphenylphosphine.⁴⁴⁷ They obtained $TcCl_4(PPh_3)_2$ which had a high magnetic moment - 3.92 B.M. at 20° and showed poor conductivity in acetone. It was unstable in polar solvents.

The isomorphous triphenylarsine complex had properties similar to the phosphorus complex. They also noted that (bisdiphenylphosphino) ethane reduced TcCl_4 in ethanol to a Tc (III) complex.

Mazzi and his co-workers reduced pertechnetate with dialkylphenylphosphines in ethanol, producing Tc (IV) and Tc (III) complexes whose yields depended on the ratio of the reactants.⁴⁶⁸ⁱ Dimethylphenylphosphine reduced pertechnetate to green $\text{trans-TcCl}_4(\text{PMe}_2\text{Ph})_2$. This complex was a non-electrolyte in nitroethane, as are the diethylphenylphosphine complex and the two corresponding bromo compounds. The magnetic moments are high - (3.4 to 3.8 BM), compatible with a metal structure having three unpaired electrons in an octahedral environment. The tetrachlorotriphenylphosphine complex, prepared in the same way, resembled the other. The monoalkyl-diphenylphosphine (Tc (IV) compounds were prepared like the others, and showed similar solubility, conductivity and magnetic properties.^{469a1}

H. Other Complexes of Tc(IV)

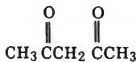


2,2'-dipyridyl

Fergusson and Hickford prepared mixed chloro-dipyridyl complexes of Tc (IV) by reacting TcCl_4 with dipyridyl in ethanol.⁴⁶⁷ⁱ They made $[\text{TcCl}_4(\text{dipy})_2]\text{Cl}_2$, which had high conductivity in dimethylformamide, and $\text{TcCl}_4(\text{dipy})$ which behaved like a weak electrolyte.

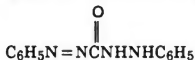
Oblova et al described the synthesis of a pyridine complex of Tc (IV).^{469b} It was prepared by heating $(\text{pyH})_2(\text{TcCl}_4)$ to 300°, forming the neutral complex $\text{TcCl}_4(\text{py})_2$. Its properties were described in a second paper.^{469d} It is cis in configuration, is isostructural with the corresponding rhenium complex, has a magnetic moment (3.91 BM) which is close to the spin-only value, and is stable to aqueous acids, aqueous alkali and various oxidizing agents. This may be due to its extreme insolubility.

Mazzi et al prepared and characterized acetylacetone complexes of Tc (IV).⁴⁷⁰ⁱ These included the tetraphenylarsonium salts of $[\text{Tc}(\text{acac})\text{Cl}_4]^{1-}$ and $[\text{Tc}(\text{acac})\text{Br}_4]^{1-}$ as well as $\text{Tc}(\text{acac})_2\text{Cl}_2$ and $\text{Tc}(\text{acac})_2\text{Br}_2$. They also prepared a mixed complex: $\text{Tc}(\text{acac})(\text{PPh}_4)\text{Br}_3$. The compounds were characterized by conductivity, magnetic susceptibility and spectra.



ACAC

Pertechnetate reacts with 1,5-diphenyl carbazide in 1.5M H_2SO_4 .⁴⁷¹ The product of the redox reactions is an uncharged complex of Tc (IV) and diphenylcarbazone. A mole ratio study showed that three moles of carbazide reacted with two moles of pertechnetate. The carbazone complex is of unknown composition. It can be extracted into CCl_4 or CHCl_3 . It has an intense absorption band at



diphenylcarbazone

520 nm ($\epsilon = 48,600 \text{ M}^{-1}\text{cm}^{-1}$). It is slow to form, and is not stable in time.

A Tc (IV) carbonato or bicarbonato complex was formed by the electrochemical reduction of $1.2 \times 10^{-4}\text{M}$ pertechnetate in 0.5M NaHCO_3 and 1M $\text{CF}_3\text{SO}_3\text{Na}$ at pH 8.⁴⁷² The reduction carried the technetium to the blue Tc (III) state, followed by rapid air oxidation to the pink Tc (IV) complex. Spectra of the Tc (III) complex showed a major peak at 630 nm ($\epsilon = 430 \text{ M}^{-1}\text{cm}^{-1}$) whereas the Tc(IV) complex had a peak at 512 nm ($\epsilon = 680 \text{ M}^{-1}\text{cm}^{-1}$).

At -0.768 volts the Tc (III) complex is formed (following the appearance of the Tc (IV) compound) and is oxidized to Tc (IV) at -0.4 volts. The couple appears to be almost reversible. The calculated E° is -1.311 V. Both complexes are anionic. The authors believe that the Tc (III) complex coordinates one more OH group than the Tc (IV) compound. The Tc (IV) complex is readily adsorbed by a strong-base anion-exchange resin.

IX.

Technetium (III) Compounds

The lower oxidation states of technetium tend to be easily inter-convertible by redox reactions, with the consequence that the assignment of a particular metal-ligand combination to a particular oxidation state becomes somewhat arbitrary. For the Tc (III) state, 7-coordinate complexes begin to appear, as do metal-metal bonds.

A. Halogen Compounds

The halides of technetium (III) are different from those in the - (IV) state and more complicated in several respects. First, they form clusters in which two technetium atoms are linked by metal to metal bonds. That is, in compounds like $(\text{Bu}_4\text{N})_2\text{Tc}_2\text{Cl}_8$ the distance between technetium atoms is less than that found in technetium metal.⁽⁴⁷³⁾ The first of these complexes is a mixed-valence compound, $(\text{NH}_4)_2\text{Tc}_2\text{Cl}_8$, containing both Tc (III) and Tc (II). It was prepared by Eakins, Humphreys and Mellish.⁽⁴⁷⁴⁾ Braton and Cotton determined the structure of this compound, its magnetic moments and its absorption spectra.⁽⁴⁷⁵⁾ It was synthesized by the reduction of $(\text{NH}_4)_2\text{TcCl}_6$ with zinc metal in hot, concentrated HCl. It is a Tc (III) - Tc (II) compound. The Tc (III)-Tc (II) cluster was made by Preetz and Peters. They reduced $(\text{NH}_4)_2\text{TcCl}_6$ with zinc and concentrated HCl, which they followed with careful dilution with an aqueous solution of tetra-n-butylammonium chloride.⁽⁴⁷⁶⁾ Cotton et al improved the synthesis and worked out the structure of the Tc (III)--Tc (III) dimer.⁽⁴⁷⁷⁾

A second difference between the Tc (III) chlorides and the halide salts of Tc (IV) and - (V) is in their reactivity. They react fairly readily with carboxylic acids, but retain the Tc_2 moiety.⁽⁴⁷⁸⁾ Attempts to prepare other complexes of Tc (III) by chloride displacement have been unsuccessful. The Tc (III) - Tc (II) (trinegative) $\text{Tc}_2\text{Cl}_8^{3-}$ disproportionates and is also readily oxidized by oxygen in HCl solution.^(479, 480)

It is safe to conclude that there is only a small likelihood that radiopharmaceutically useful complexes will be prepared from the Tc (III) cluster compounds, particularly at low technetium concentrations.

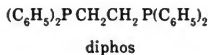
B. Thiourea Complexes

An orange complex of undetermined composition was formed in the reaction of pertechnetate with thiourea in 2N nitric acid.⁽⁴⁸¹⁾ Beckmann and Lederer concluded that it was a Tc (IV) complex because the absorption spectrum of the reaction mixture of pertechnetate and thiourea in HCl solution closely resembled that of TcCl_6^{2-} .⁽⁴⁸²⁾ They did not consider the possibility of further reduction by the thiourea itself. Morpugo maintained that unstable products from the reaction of pertechnetate, thiourea and SnCl_4 (in acid) were compounds of Tc (V).⁽⁴⁸³⁾ Kopunec et al concluded that a thiourea complex (stabilized with two moles of thiourea per mole of technetium) was formed by way of an intermediate cationic species.⁽⁴⁸⁴⁾ The complex itself (i.e., the final product) was later found to be

cationic by its uptake on a cation-exchange resin and by its extraction into an organic solvent by means of a cobalt (III) anionic reagent.^{1485f}

Definitive research on the technetium oxidation state, the composition, the structure and various chemical properties of the technetium-thiourea complex was carried out by Abrams et al.¹⁴⁸⁶ They prepared both the trichloride, hexakis (thiourea-S) technetium (III) $\text{Cl}_3 [\text{Tc}(\text{tu-S})_6 \text{Cl}_3]$, where tu stands for thiourea and the tetrafluoroborate, $[\text{Tc}(\text{tu-S})_6] (\text{BF}_4)_3$ by reacting thiourea with pertechnetate in ethanol containing either HCl or HBF_4 . The absorption spectrum in methanol showed peaks at 493 nm, 428 nm and 233 nm for both salts, but the absorptivity coefficients were different. The fluoroborate showed consistently higher coefficients. The conductivities of the chloride in methanol and the tetrafluoro-borate in acetonitrile were those expected of 3:1 electrolytes. The magnetic moments were both about 2.7 μB (μeff). The structure of the trichloride was determined. The technetium was approximately octahedrally coordinated by the six sulfur atoms of the thiourea ligands, which in turn were almost planar. There was extensive H-bonding throughout the solid structure, none to the sulfur atoms.

The most important aspect of its chemistry for nuclear medicine is the ease with which the thiourea can be displaced by other ligands. In this sense the complex cation does for Tc (III) and lower oxidation states what the halide complexes TcCl_6^{3-} and TcOCl_4^{1-} do for Tc (IV) and Tc (V) compound synthesis. Thus, the dichlorobis (1,2-bis (diphenylphosphino) ethane) technetium (III) chloride, $([\text{Tc}(\text{diphos})_2 \text{Cl}_2 \text{Cl}_2 \cdot 2\text{H}_2\text{O}])$ was prepared in HCl methanol. The hexakis (t-butyl isocyanide) technetium (I)



hexafluophosphate and the hexakis (trimethylphosphite) technetium (I) hexafluophosphate were similarly prepared (with attendant reduction), as was an otherwise uncharacterized DTPA complex, and the $[\text{Tc}(\text{NCS})_6]^{3-}$ complex.

Muenze and Grossmann reported that it was possible to form various Tc (III) complexes by ligand displacement of thiourea groups.^{1487a} They also reported that the pentakis chloro complex of Tc (III) could react with dippe [(diphenylphosphino) ethane] to form $[\text{TcCl}_4(\text{dippe})_2]^+$ in 0.48N HCl, and at a Tc: dippe ratio of 1:13. In 0.96 N HCl they found tetrakis dichloro Tc (III) (i.e. $[\text{TcL}_2\text{Cl}_2]^+$). At much higher ratios of Tc to dippe they reported that TcCl_6^{3-} formed. In this research they isolated one previously known compound: $[\text{TcCl}_4(\text{dippe})_2]\text{Cl}$.

C. Aminocarboxylate Complexes

The reduction of pertechnetate-99 by excess SnCl_2 in the presence of DTPA produced a Tc (III) complex. This conclusion was based on a polarographic analysis of unreacted Sn (II). The complex was not otherwise characterized.¹⁴⁸² The chemistry of Tc (III) aminocarboxylate complexes involves Tc dimer formation, as Linder has demonstrated, but the Tc (III) -O-Tc (III) compounds have not been investigated as thoroughly as the mixed-valence Tc (III)-O-Tc (IV) entities.¹⁴⁴¹

Russell and Speiser studied the electrochemistry of a number of aminocarboxylate complexes of technetium by polarography.^{1487b} The ligands included DTPA, EDTA, ADA (N-(2-acetamido) iminodiacetate) and HIDA (N-(2,6-dimethylphenylcarbamoyl methyl) iminodiacetic acid). In acid solution the electron number, n, was 4; Tc (III) was formed in all cases. The electron number gradually increased with increasing pH. Coulometry in a 3mM TcO_4^- solution at pH 6 with 0.1M DTPA produced a brown color (presumably TcO_3), but cutting the pertechnetate concentration in half showed

$n=4$. Amperometric titrations with SnCl_2 were carried out on the various solutions with a dropping mercury electrode. The Sn(II) anodic wave was reported to give results concordant with the cathodic Tc wave. In acid solution, n values between 3 & 4 were found for DTPA, EDTA and ADA. In alkaline solutions of all the ligands, three-electron reductions to Tc(IV) were found, as well as in neutral DTPA and EDTA solutions. The amperometric titrations in acid solution gave the same non-integral values of n at the end-points which had been reported by Steigman et al in the direct titration of pertechnetate by SnCl_2 in a pH 4 solution of DTPA.²⁵² The more relevant information for radiopharmaceutical purposes would have been the n values obtained with an excess of SnCl_2 . The results obtained in alkali should be accepted with caution because of the instability of various DTPA and EDTA complexes in basic solution.^{468,469}

D. Acetylacetone (acac) Complexes

There are mixed ligand complexes of Tc(III) which contain acetylacetone. All will be reported in this section although they could readily be termed mixed phosphine complexes.

The tris acac complex Tc(acac)_3 was prepared by heating $\text{TcCl}_3(\text{PPh}_3)_3$ in acetylacetone under nitrogen for 18 hours.⁴⁷⁰ It is a dark violet solid, stable as crystals or in solution, soluble in polar organic solvents but poorly soluble in diethyl ether and in pentane. Its magnetic moment is about 2.7 BM, suggesting that there are two unpaired electrons on the technetium, in a d^4 configuration. It is non-conducting in dichloromethane solution. There is a later report of a synthesis in which NH_4TcO_4 was refluxed in acetylacetone as solvent. No further details are available.⁴⁹⁰

The synthesis of various halo-acac complexes of Tc(IV) was described in the Tc(IV) section.⁴⁷⁰ The same reference contains synthesis of five mixed acac-halide or acac-triphenylphosphine complexes of Tc(III). In general these were prepared from Tc(IV) $\text{Cl}_4(\text{PPh}_3)_2$ and acac under more forcing conditions of mole ratio and temperature than those used in the Tc(IV) mixed ligand preparations. The reactions are complicated, and different conditions produced different products. These include $\text{TcX}_2(\text{acac})(\text{PPh}_3)_2$ red complexes which are stable in air but decompose in a number of organic solvents and have high magnetic moments ($\mu_{\text{eff.}} = 3.1\text{--}3.3$ BM). The $\text{TcX}(\text{acac})_2(\text{PPh}_3)$ compounds are yellow-orange, stable, soluble in many polar solvents, and are non-conducting. The magnetic moments ($\mu_{\text{eff.}} = 2.7\text{--}2.8$ BM) are those expected of a d^4 compound with an octahedral configuration. (The symbol X stands for Cl or Br). Details are given of three methods of synthesis: (1) $\text{TcCl}_4(\text{PPh}_3)_2$ and acac in benzene, (2) refluxing the same compound in acac, and (3) reacting $(\text{NH}_4)_2\text{TcCl}_6$ with a solution of triphenylphosphine in acetylacetone as solvent. Compound characterizations were by IR and electronic spectra, chemical analysis, and magnetic moments.⁴⁷⁰

$\text{Tc(X)(acac)}_2\text{PPh}_3$ has two crystalline forms. The halogen is trans to the phosphine.⁴⁹¹ It was prepared by heating trans-tetrachlorobis(triphenylphosphino) technetium(IV) in anhydrous acac.⁴⁷² The technetium has a distorted octahedral configuration.

E. Phosphine and Arsine Complexes

All phosphine and arsine complexes of technetium(III) are mixed-ligand complexes. The simplest of these are the arsine-halogen or phosphine-halogen compounds.

1. Phosphine-Halogen and Arsine-Halogen Complexes

The first Tc(III) compound of this type was isolated in 1959 by Fergusson and Nyholm.⁴⁹³ Following earlier work with rhenium, they reacted K_2TcCl_6 with bis-orthophenylene-bis-dimethylarsine in acidic aqueous alcohol, reducing and complexing the technetium to form trans-dichloro-bis(orthophenylene-bis-dimethylarsine) Tc(III) chloride. This was the source of the corresponding trans-dibromo bromide after reaction with LiBr in alcohol. Similarly the bromo compound yielded the trans-diiodo iodide after treatment with LiI in the same solvent. The complexes

were stable. Their magnetic moments were 2.7, 3.2 and 3.4 BM respectively, pointing to a d^4 configuration (two unpaired electrons). It was concluded that they were 1:1 electrolytes from conductivity measurements in nitromethane.

The structures of the chloride and perchlorate salts of the trans-dichloro complex were determined from X-ray diffraction.⁴⁹⁴ Both compounds show 6-coordinate technetium, with trans chloro ligands, and with two almost co-planar o-phenylene bis(dimethylarsine) groups. The Tc-Cl distance is virtually the same in these complexes, in $(\text{NH}_4)_2 \text{TcCl}_6$ and in $\text{Bu}_4\text{N}(\text{TcOCl}_4)$ - that is, in Tc (III), Tc (IV) and Tc (V) halo complexes.

Fergusson and Nyholm reacted the orange Tc (III) chloride with chlorine, changing it to a brown 8-coordinate Tc (V) complex - $[\text{Tc}(\text{diars})_2\text{Cl}_2]\text{ClO}_4$.⁴⁹⁵ The magnetic moment was 0.9 BM at room temperature. The conductivity in organic solvents was that of a 1:1 electrolyte.

The coordination and the structure of the pentavalent compound were determined by X-ray diffraction.⁴⁹⁴ The cation had D_{2h} dodecahedral coordination. The stability of the 8-coordinate complex was attributed to the formation of a closed-shell compound with 18 valence electrons from one with an open-shell 16 electron arrangement.⁴⁹⁶

Phosphine complexes of Tc (III) were prepared by Fergusson and Hickford.⁴⁹⁷ They heated TcCl_3 in ethanol with (bisdiethylphosphine) ethane and obtained dichlorobis-(bisdiethylphosphine) ethane-technetium (III) chloride. The red-orange compound had a magnetic moment of 2.68 BM and showed the conductivity of a 1:1 electrolyte in nitromethane. It was isomorphous with the corresponding Re (III) complex.⁴⁹⁸

Mazzi et al later reported that with a large excess (5:1) of dimethylphenylphosphine over pertechnetate in ethanol they obtained complexes of the type $\text{TcX}_3(\text{PMe}_2\text{Ph})_3$ ($\text{X}=\text{Cl}, \text{Br}$).⁴⁹⁹ It was concluded from the infrared spectra that the compounds had the mer configuration. Mer-trichloro tris(dimethylphenylphosphine) technetium (III) was prepared by reducing either NH_4TcO_4 or $(\text{NH}_4)_2\text{TcCl}_6$ with the phosphine in ethanol.⁵⁰⁰ Compounds were characterized by elemental analysis, magnetic susceptibility, infrared and H-NMR spectroscopy, and X-ray diffraction. The technetium complex geometry was consistent with those of the corresponding trivalent Re, Os and Ir compounds. The Tc coordination was distorted octahedral. Two pairs of like ligands were trans, leaving the remaining phosphorus atom trans to chlorine.

Other Tc (III) phosphine complexes with different ligands were prepared by phosphine reduction of pertechnetate.⁵⁰¹ These included mer-trichloro tris(methyldiethylphosphine) technetium (III), the tribromo compound and the trichloro and tribromo complexes of technetium (III) with $(\text{PEtPh})_3$. These were characterized by electronic and IR spectra and by elemental analysis. From this series it was learned that the alkylphenylphosphine complexes of Tc (III) formed readily, but decomposed more quickly than the dialkylphenylphosphine analogues. The difference in stability was attributed to steric effects of the ligands.

Fergusson and Hevelldt prepared $[\text{Tc}^{111}\text{Cl}_4(\text{Et}_2\text{PhP})_2]$ among other complexes.⁵⁰² They reacted $\text{TcCl}_3(\text{Ph}_3\text{P})_2$ with Et_2PhP . The latter reduced the technetium to the (III) state, and displaced the triphenylphosphine ligand and a chlorine atom. A similar reduction procedure was later used to prepare the bis(1,2-dimethylphosphine) ethane complex, $[\text{TcX}_3(\text{dmpe})_2]^+$ as the trifluoromethane sulfonate salt.⁵⁰³

Mazzi et al investigated the electrochemistry of technetium phosphine complexes in order to evaluate the effects of π -acceptor ligands in acetonitrile. The first paper of this series examined the oxidation of $\text{TcCl}_3(\text{PMe}_2\text{Ph})_3$.⁵⁰⁴ On oxidation $\text{TcCl}_3(\text{PMe}_2\text{Ph})_3$ was formed if NaClO_4 was the supporting electrolyte, and $[\text{TcCl}_2(\text{PMe}_2\text{Ph})_3\text{MeCN}]^+\text{ClO}_4^-$ was the product if $n\text{-Bu}_4\text{N}^+\text{ClO}_4^-$ was the electrolyte. In either case it was assumed that the primary electrochemically formed species was

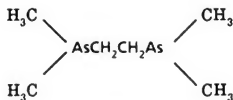
$[\text{TcCl}_3(\text{PMe}_2\text{Ph})_3]^+ \text{ClO}_4^-$ a Tc (IV) cation. If sodium ions were present, NaCl was precipitated and the final product was a Tc (III) complex, $[\text{TcCl}_2(\text{PMe}_2\text{Ph})_3(\text{MeCN})]^+ \text{ClO}_4^-$ with traces of water acting as reductant, and producing oxygen. In the presence of the quaternary ammonium perchlorate it was hypothesized that the initially formed Tc (IV) cation reacted with chloride ions (which originated in side reactions) to yield $\text{TcCl}_4(\text{PMe}_2\text{Ph})_2$.

A second paper described the reduction of halophosphine complexes.⁵⁰⁵ The reduction of $\text{TcCl}_3(\text{PMe}_2\text{Ph})_3$ in acetonitrile yielded $[\text{TcCl}_2(\text{PMe}_2\text{Ph})_3(\text{MeCN})]^+ \text{Cl}^-$, following an initial electrochemical reduction. At a more negative potential there was further reduction, yielding $\text{TcCl}(\text{PMe}_2\text{Ph})_3(\text{MeCN})_2$, that is, a Tc (II) complex followed by a Tc (I) complex. The reactions were believed to be of the e.c.e. type - i.e., a chemical step following and preceding electrochemical steps.⁵⁰⁶ The entry of acetonitrile molecules and the expulsion of chloride ligands may involve the formation of a 7-coordinate Tc (II) compound as an intermediate. The chemistry of these compounds is obviously complicated. With respect to the reduction of the Tc (IV) complex $\text{TcCl}_4(\text{PMe}_2\text{Ph})_2$, there is a 1-electron reduction, and the main product is $\text{TcCl}_3(\text{PMe}_2\text{Ph})_2$.

A large body of chemical information about mixed phosphine and arsine complexes of Tc (III) has been accumulated in the course of a search for cationic Tc complexes which might be useful in heart imaging. These are of the type $\text{trans}[\text{TcD}_2\text{X}_2]^+$, in which D represents a chelating diphosphine ligand, and X represents a halogen. Libson, Barnett and Deutsch systematically investigated the synthesis of nine of these complexes, varying the nature of the phosphine or arsine ligand and of the halogen, and characterized the resulting compounds by a variety of techniques, including structural and electrochemical methods.⁵⁰⁷ The halogen and halogen-like ligands included Cl, Br and SCN⁻. The organic ligands included DPPE (1,2 bis-diphenylphosphino) ethane and several variants, DMPE (bis (1,2-dimethylphosphino) ethane, and DIARS (o-phenylene bis (dimethylarsine)). The favored preparations involved the reduction of pertechnetate or TcX_6^{3-} by excess phosphine or arsine ligand. Structural analysis showed that in the DPPE complex the technetium was central and octahedral, coordinated with 4 equatorial phosphorus atoms and two trans-axial halogen atoms.



DMPE



DIARS

The electrochemistry of these compounds was carried out by cyclic voltammetry in dimethylformamide (as Mazzi had shown), with gold, platinum and glassy carbon electrodes. It was concluded that complexes with Cl or Br were robust (i.e. hard to displace). The E° values of the various complexes depended on the nature of both ligands. The Br complexes were stronger oxidants than the Cl compounds. Aryl substituents on phosphorus gave stronger oxidants than alkyl residues. Both the Tc (III)-(II) and the Tc (II)-(I) equilibria were reversible in this medium. There was no indication of a Tc (IV)-(III) wave.

A second paper dealt with the redox chemistry of the Tc (III) D_2X_2^+ cations (and the Tc (I) D_2^+ cations).⁵⁰⁸ Spectroelectrochemistry was added to the usual electrochemical measurements. The Tc D_2X_2^+ complexes in DMF showed two reversible changes, corresponding to two 1-electron reversible reactions forming Tc (II) and Tc (I). Conventional pulse polarography was also performed in aqueous solution for $\text{TcD}_2\text{X}_2^{+0}$ (i.e., Tc (III) cation and Tc (II) neutral product). The supporting electrolyte was

0.5 M KNO₃. The E' value in this solution was -0.122 volts (vs NHE) for the DMPE chloride and -0.016 volts for the dibromo complex. These values were much more positive, by several hundred millivolts, than the values expected from the measurements in DMF. In the case of the DEPE complexes, the differences were about 350 millivolts more positive than the values in DMF. The differences were attributed to the insolubility in water of the reduced form, which would make it easier to reduce the Tc(III) complex. Such a facilitated reduction could be expected to take place in biological media as well.

Even assuming that the reduction of the Tc (III) complex and the re-oxidation of the Tc (II) insoluble form together are reversible in the time frame of normal pulse polarography, it does not follow that in the high dilution encountered in Tc-99m solutions and in the biological media (i.e. blood) the same considerations, i.e., reversible equilibrium influenced by the insolubility of one reactant-will apply. In the first pass the concentration of the Tc (III) complex is about 10⁻⁸M. In subsequent passes it will be much less. The neutral Tc (II) complex may be soluble at those levels of concentration, which would make the reduction process more difficult. There is the possibility that the insoluble Tc (II) complex would be solubilized by proteins or cholate salts or similar solubilizing agents. In addition, the mechanisms of reduction by biological molecules (presumably those carrying sulfhydryl groups) are often complicated. In particular it is quite possible that the reduction by a thiol group, producing a thiol radical, may not be reversible. If this is the case, the insolubility of the Tc (II) complex in water will not contribute to rendering the reduction of the Tc (III) complex easier. A direct demonstration of such a reduction could have been made.

2. Phosphine-Schiff Base Complexes

Nine compounds of Tc (III) with tertiary phosphines and Schiff bases were prepared and studied.⁵⁰⁹ The bases included (acac)₃en(1), triac₂en(2), brac₂en(3) and sal₂en(4):

- (1) N,N'-ethylene bis (acetylacetone iminato)
- (2) N,N'-ethylene bis (tert-butyl acetoacetate iminato)
- (3) N,N'-ethylene bis (3-bromoacetylacetone iminato)
- (4) N,N'-ethylene bis (salicylidene iminato).

The preparations are described, and the crystal structure of the title compound was determined. The Tc (III) is octahedrally coordinated in the center with two N and two O atoms of the Schiff base in equatorial positions and two phosphorus atoms in the trans apical positions.

The phosphine structures were also varied: triethyl, diethyl phenyl, diphenyl ethyl, and triphenyl were studied. Spectra, analyses and polarographic behavior were recorded. E' values in acetonitrile were determined by cyclic voltammetry, using a silver-silver chloride reference electrode. The E' values ranged from -1.050 volts to -0.670 volts in the series for the reduction Tc(III) → Tc(II). With a glassy carbon electrode, the reactions were not quite electrochemically reversible.

In a related study, eight similar compounds with the same tetradentate Schiff bases and slightly different phosphines were studied in propylene carbonate solution by cyclic voltammetry.⁵¹⁰ Here all compounds showed reversible behavior on platinum for both the oxidation to Tc (IV) and the reduction to Tc (II). The reduction potentials ranged from -1.108V (vs Ag-AgCl/3M NaCl) for the trans [Tc P (Et)₃(acac₂en)]⁺ to -0.693 V for trans [Tc (PEt Ph)₃(Sal₂en)]⁺. The differences were evaluated in terms of π acidity and σ donor ability. There is no indication of the suitability of the more difficult-to-reduce Tc (III) complexes for heart imaging although the myocardial washout is decreased.^{510a}

3. Mixed Phosphine - Thio Complexes

A mixed complex of Tc (III) containing technetium-sulfur bonds was prepared by Lorenz and Schmidt.⁽⁵¹³⁾ They reacted the trichlorotris dimethylphenylphosphine technetium (III) complex in acetone with Na_2S , CNEt_3 , $\cdot 3\text{H}_2\text{O}$ (sodium diethyldithiocarbamate) and displaced the three halogen atoms and two of the phosphine ligands. The new complex - tris (diethyl (dithiocarbamate) - dimethyl phenyl-phosphine technetium (III) was characterized by X-ray diffraction and IR, electronic and H-NMR spectroscopy. Its coordination number is 7. The configuration was pentagonal-bipyramidal. A similar compound was obtained from the reaction between the same starting Tc (III) complex and 1,2-dicyanoethylenedithiolate in acetone, and was precipitated as the tetraphenyl-arsonium salt. The detailed reactions and the crystal structure of the first complex were reported in another paper.⁽⁵¹²⁾ Two dithiocarbamate ligands are in the equatorial plane and the third ligand has one S atom in the equatorial and the second S atom in an axial position. The Tc-P distance, 2.330 Å, is much shorter than that encountered in other phosphine complexes. The complex is easily oxidized by dissolving it in acetone and adding concentrated HCl .⁽⁵¹³⁾ The oxidized product was isolated as the hexafluoro phosphate salt of the Tc (IV) cation, which apparently maintained the 7-coordinate chemistry after the oxidation. In acetone this salt showed the conductivity characteristic of a 1:1 electrolyte in that medium.

4. Mixed Phosphine - Carbon Monoxide Complexes

Mixed Tc (III) phosphorus complexes containing carbon monoxide were prepared from existing tertiary phosphine complexes or similar compounds.⁽⁵¹⁴⁾ The reference deals with phosphonite rather than phosphine complexes, but the chemistries are similar; they are both reducing agents and complexing agents for technetium. Mazzi et al refluxed an ethanol solution of the mer $[\text{TcCl}_3(\text{PMe}_2\text{Ph})_3]$ complex under CO at 1 atmosphere, and obtained the first Tc C_{3v} 7-coordinate compound $[\text{TcCl}_3(\text{CO})(\text{PMe}_2\text{Ph})_2]$. The pale yellow complex is stable in air, and is soluble in polar solvents. The projected coordination number was later confirmed.⁽⁵¹⁵⁾

5. Mixed Hydrido - Phosphine Complexes

A mixed hydride-phosphine-chloro complex of technetium (III) has been reported.⁽⁵¹⁶⁾ $[\text{TcCl}_2\text{L}_2]$ (L = 1,2-bis diphenylphosphino ethane) was refluxed with LiAlH_4 in tetrahydrofuran under an argon atmosphere for 30 hours. The addition of ethanol precipitated yellow crystals. The complex was characterized by elemental analysis, IR spectra and proton NMR. The IR spectrum showed bands at 1775 cm^{-1} and 1851 cm^{-1} which were assigned to Tc-H stretching vibrations. The NMR pattern showed hydride H atoms at -6.9 ppm. The compound was assigned the composition $(\text{H}_2\text{Cl}_2\text{Tc}(\text{III}))$. The reaction was explained as the replacement of chloride by one hydride, and the addition of a second atom of hydrogen to the metal. The technetium appears to be 7-coordinate, which is known to be the case for the corresponding rhenium compound.⁽⁵¹⁷⁾

F. Cyanide Complexes

Potassium heptacyanotechnetate (III) was prepared from $(\text{NH}_4)_2\text{TcCl}_6$ in methanol and aqueous KCN , in the absence of air,⁽⁵¹⁸⁾ in the same manner as the rhenium complex.⁽⁵¹⁹⁾ The reduction is presumed to be due to the iodide ion. A yellow-orange crystalline solid, $\text{K}_2\text{Tc}(\text{CN})_7 \cdot 2\text{H}_2\text{O}$, was obtained. It was the second 7-coordinate technetium complex reported.⁽⁵¹²⁾ Its coordination geometry was deduced from an analysis of its IR and Raman spectra. It was concluded that it was a pentagonal bipyramid, unlike the previously reported seven-coordinate Tc (III) complex, which was a monocoordinated octahedron. The cyanide complex is diamagnetic. It undergoes slow decomposition in oxygen-containing water. On recrystallization from aerobic methanol-water solution the product is $\text{K}_2\text{TcO}(\text{CN})_5 \cdot 4\text{H}_2\text{O}$, a Tc (V) complex.

G. Thiocyanate Complexes

The analytical section has an extensive discussion of the Tc (V) - IV and - (III) thiocyanate complexes. A detailed study of the Tc (III) and - (IV) compounds, including their structures, was carried out.⁽³²¹⁾ The tetra-n-butylammonium hexakis (isothiocyanato) technetate (III) was prepared by reducing $(\text{NH}_4)_2\text{TcBr}_6$ in methanol with hydrazine hydrate in the presence of NH_4SCN , followed by precipitation of the air-sensitive quaternary ammonium salt.⁽³²⁰⁾ This is the same procedure which was used in an earlier report, in which the complex was mistakenly described as a seven-coordinate compound.⁽³²¹⁾ $(\text{Bu}_4\text{N})_3[\text{Tc}(\text{SCN})_6]$ has a magnetic moment of 3.0 - 3.3 BM at room temperature. The conductivity in acetonitrile is that expected of a 3:1 electrolyte. The cathodic half-wave potential in the same solvent was - 1.09 volts versus standard calomel, and was irreversible, whereas the anodic potential was reversible at + 0.18 volts. The principal electronic band was at 403 nm in methanol ($\epsilon = 19,400 \text{ ML}^{-1}\text{cm}^{-1}$) and was shifted to 412 nm in acetonitrile ($\epsilon = 25,800$). The Tc (III) complex could be oxidized to the Tc (IV) state by thiocyanogen or by NO. X-ray diffraction showed that the Tc atom in the quaternary ammonium salt had approximately octahedral symmetry. The organic cations are packed in a roughly body - centered arrangement. The six Tc-N distances are 2.04 or 2.05 Å.

H. Oxime Complexes of Technetium (III)

Unlike most of the technetium chemical literature, in which similar work had already been carried out on rhenium compounds, there is very little on the reactions of rhenium compounds with oximes, except for analytical determinations. A number of spectrophotometric analytical procedures based on the reduction of perrhenate, usually by acid SnCl_2 in the presence of oximes, are in the literature, but there are few investigations of composition, oxidation state, etc. Meloche et al, working with α -furildioxime, reported that Re (IV) did not react with the oxime unless SnCl_2 was added, and that an electrolytic reduction of perrhenate in the presence of the oxime was ineffective, as were a number of reducing agents other than SnCl_2 .⁽³²²⁾ Narayanan and Umland examined the stoichiometry of the reaction between SnCl_2 and reduced perrhenate in the presence of dimethylglyoxime.⁽³²³⁾ They concluded that in 1:1 methanol-acetic acid solution there were three DMG moieties per rhenium, but that in aqueous HCl the stoichiometry was 2:1. In the light of more recent technetium investigations, the latter value is dubious. Apart from a number of successful assays for rhenium with various oximes (and all used acidic SnCl_2 solutions!), there were no additional investigations on even the stoichiometries of the formed complexes.

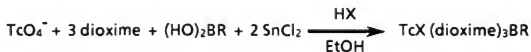
There have been several assays for technetium based on oxime complexation.^(481, 524) The first more complete investigation of the reaction between reduced technetium and dimethylglyoxime in the presence of SnCl_2 was reported by Deutsch et al.⁽³²²⁾ These workers had obtained both a yellow and a brown crystalline compound by reacting SnCl_2 in HCl with pertechnetate in 95% ethanol saturated with dimethylglyoxime. After several weeks at room temperature less than a milligram of the yellow product was obtained. This showed the Tc:Sn:Cl ratio to be 1:1:3; the diffraction pattern showed the Tc and Sn atoms joined by an oxygen bridge, and two N-O bridges. The technetium was 7 - coordinate, and the tin had octahedral coordination. The tin was believed to be in the (IV) state, and the technetium was thought to be Tc (V). In effect, the tin served to cap the trigonal prismatic structure around the technetium. This capping explains the findings of Meloche et al, that SnCl_2 was unique among the reducing agents in the formation of a reduced perrhenate complex with α -furildioxime.⁽³²²⁾

The same Tc complex was re-investigated by Linder et al⁽⁵²⁵⁾ as part of a more general inquiry into technetium dioxime complexes capped with various derivatives of boric acid. They found that they could prepare the same complex reported by Deutsch et al, but in good (50%) yield simply by adding two equivalents of SnCl_2 to a refluxing HCl-alcohol solution of DMG and NH_4TeO_4 . The complex is diamagnetic, as previously reported, and is neutral. These workers concluded, however, that it was not a Tc (V) complex, but rather a Tc(III) compound. The mass spectral analysis (FAB spectrum) showed a strong molecular ion with a major peak at m/c of 685. This corresponds to a Tc (III) compound with 4 protons for charge balance. If it were a Tc (V) compound it would require only two

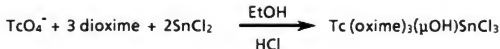
protons for charge balance, with $m/e = 683$. This was not seen. While it is possible that the Tc (V) compound was readily reduced in the mass spectrometer, chemical reaction pointed to a Tc (III) complex. In the absence of reducing agents, the complex is readily changed to other Tc (III) oxime species, including $\text{TcCl}(\text{DMG})_3$ and $\text{TcCl}(\text{DMG})_2\text{BR}$ (BR stands for boronic aryl or alkyl acids). Finally, if the Tc (III) complex $\text{TcCl}(\text{DMG})_3$ is treated with SnCl_4 in ethanol, the original compound, Tc (DMG) $_3\mu\text{-OH SnCl}_3$, is quantitatively reformed.

Research at the Squibb Institute for Medical Research has produced a class of neutral technetium (III) compounds derived from tris oxime complexes, and capped with boronic acids. The compounds, whose Tc-99m analogs show brain or heart uptake, are called BATO's (for boronic acid adducts of technetium dioxime complexes).⁽⁵²⁶⁾ The compounds included [Bis[1,2-cyclohexanedione dioximate (1-)-O]-[1,2-cyclohexanedione dioximate (2-)-O] borato (2-N,N',N'',N''',N''',N''')-chlorotechnetium (SQ 32014) and Bis [1,2-cyclohexanedione dioximate (1-)-O]-[1,2-cyclohexanedione dioximate (2-)-O] methylborato (2-)-N,N',N'',N''',N''',N''')-chlorotechnetium (SQ 30,217), in both of which the dioxime was cyclohexanedione dioxime. A later arrival, SQ 32,097, was based on dimethylglyoxime: [Bis [2,3-butanedione dioximate (1-)-O]-[2,3-butanedione dioximate (2-)-O] 2-methyl, 1-propyl borato (2-)-N,N',N'',N''',N''',N''')-chlorotechnetium.⁽⁵²⁷⁾ The complexes were characterized by X-ray crystallography, conductivity, elemental analysis, HPLC, infra-red, NMR and UV-visible spectra, lipophilicity, and a wide-variety of mass spectra. In the cyclohexanedione complexes, the technetium was coordinated to 3 N-bonded dioxime molecules, and to one Cl atom in an axial position. The technetium has a monocapped distorted trigonal prismatic geometry. At one end of the molecule the dioxime groups are held together by a proton bridge in which 2 H atoms are shared by 3 O atoms. The other end of the molecule is held together by a methylboron cap through the remaining 3 O atoms of the oxime groups. The dimethylglyoximate complex, which was also exhaustively characterized, is quite similar in structure to the other two, with a 7-coordinate Tc(III) atom capped with boron at one end, and holding 2 proton bridges at the other end.⁽⁵²⁷⁾

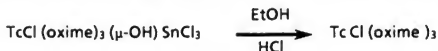
The preparation of these complexes involved a template synthesis in which the dioxime, the boronic acid derivative, pertechnetate and the reducing agent (usually Sn^{2+}) are combined to produce the BATO:



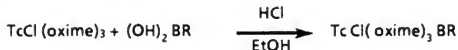
In more recent work, neutral intermediates were found to form in the absence of boronic acids.⁽⁵²⁸⁾



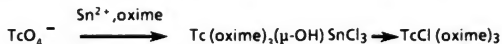
The tin serves as a cap. In the absence of tin, the complexes are unstable. In acid solution without excess stannous ion, the tin cap is lost, and the neutral Tc (III) complex, $\text{TcCl}(\text{oxime})_3$, is formed:



The DMG complex, $\text{TcCl}(\text{DMG})_3$, has been characterized by X-ray crystallography. It is a 7-coordinate neutral Tc(III) compound. Either tin-free tris oxime complex is readily converted to the Tc(III) BATO complex by treatment with a boronic acid:



The tin-capped oxime complexes are also readily converted to the corresponding BATO complexes by reaction with a boronic acid. This suggests the following reaction scheme:



The BATO complexes are robust - that is they are resistant to oxidation, reduction or metal exchange. However, the axial chloride is readily replaced in water by a hydroxy group. The rates of exchange of four complexes were determined in three solutions of different pH (all, however, near 7) and at two temperatures (both near room temperature).⁽⁵²⁹⁾ The exchange rate is measured in minutes to slightly more than one hour for the half-times, suggesting that the interchange does not take place immediately on injection.

The hydroxy compound in general resembles the parent chloro compound, except for decreased lipophilicity.

X.

Technetium (II) Compounds

The complexes of Tc (II) (and of Tc (I)) are characterized by the same metal-to-metal bond formation seen in some Tc (III) compounds, by the facile redox interconvertibility in one or both directions and by their stabilization in the low oxidation states through π back-bonding by π acceptor ligands like NO, CO, and phosphorus and arsenic compounds.

A. Chloro Complexes and Related Compounds

The preceding section has already dealt with the formation and some chemical properties of Tc (III) and Tc (II), (III) in Tc-Tc compounds. A chloride of lower oxidation state was first prepared by Eakins, Humphreys and Mellish by reducing NH_4TcO_4 with zinc metal in hot, concentrated HCl.⁴⁷⁴ They obtained $(\text{NH}_4)_3\text{Tc}_2\text{Cl}_8$, whose structure and Tc-Tc bond distance were established by Cotton and Bratten.⁵³⁰ These authors oxidized the compound directly to a salt of the TcCl_6^{2-} anion. There was no evidence of a stable intermediate. The one electron in excess of a stable (8-electron) quadruple Tc-Tc bond has proved to be difficult to remove, so that the $\text{Tc}_2\text{Cl}_8^{2-}$ anion has not yet been produced. One ditechneum (III) compound with a quadruple bond - $\text{Tc}_2(\text{O}_3\text{CCMe})_2\text{Cl}_2$ - was synthesized in very small yield.⁵³¹ An attempt to produce a similar compound was undertaken by reacting $(\text{NH}_4)_3\text{Tc}_2\text{Cl}_8$ with 2-hydroxypyridine.⁵³² The resulting uncharged compound was insoluble in all solvents which were tried, but had the Tc oxidation state 2.5 and the bond order 3.5.

The structure of $\text{K}_3\text{Tc}_2\text{Cl}_8 \cdot n\text{H}_2\text{O}$ was solved in 1975.⁵³³ The $\text{Tc}_2\text{Cl}_8^{2-}$ anion has a structure similar to $\text{Re}_2\text{Cl}_8^{2-}$. Four chlorine atoms and one technetium atom make up the coordination sphere of each Tc atom, which is a square pyramid. Each Tc atom has a vacant axial coordination site. The compound is isostructural with the previously reported $(\text{NH}_4)_3\text{Tc}_2\text{Cl}_8 \cdot 2\text{H}_2\text{O}$.

B. Phosphine and Arsine Complexes

The di-*o*-phenylenebis (dimethylarsino) diiodo complex of Tc (II) was obtained by Fergusson and Nyholm in 1959.⁴⁹³ They reacted the corresponding Tc (III) complex, $[\text{Tc}^{\text{III}}(\text{di-}t\text{-arsine})_2\text{I}]^+ \text{I}^-$ with SO_2 , or refluxed it in ethanol. They obtained brown crystals whose magnetic moment (μ_{eff}) was approximately 3.0. It was isomorphous with the corresponding rhenium complex. It was a non-electrolyte in both nitromethane and nitrobenzene.

Fergusson and Hickford prepared Tc (II) complexes of 1,2-bis- (diphenylphosphino) ethane (dppe) of the type $[\text{Tc}(\text{dppe})_2\text{X}_2]$ in which X represents Br or Cl.⁴⁹⁷ These were prepared by reducing the corresponding Tc (III) complexes with sodium borohydride in alcohol-water solution. The magnetic moments were 2.05 (Cl) and 2.28 (Br). Both Tc (II) complexes (i.e., Br & Cl) were soluble in

benzene and in DMF. The chloro compound was only slightly soluble in water. HNO_3 easily oxidized the two compounds to the trivalent complexes.

Libson, Barnett and Deutsch systematically investigated the spectral and electrochemical properties of the Tc (III) and Tc (II) complexes of the arsines and phosphines reported above, and also prepared the $[\text{Tc}^{\text{II}}(\text{DPPE})_2(\text{NCS})_2]^0$ complex.⁵⁰⁷ The latter complex was unusual in that it was stable, unlike its chloro- and bromo- analogues, which are more stable in the Tc (III) state. This was also examined by Bandoli et al, who worked out the crystal structure of the compound and established that the NCS ligands were N-bonded and not S-bonded to the metal.⁵³⁴ This bonding was in apparent contradiction to the principle of symbiosis which states that in octahedral complexes the presence of soft ligands should promote the addition of other soft ligands (-SCN bonding rather than -NCS bonding).⁵³⁵ However, exceptions to this rule have been observed.⁵³⁶ The reasons for these exceptions are not well understood. The importance of the thiocyanato complex is that its stability emphasizes the importance of π -electron back-bonding (from technetium) in the stabilization of lower-valent technetium complexes, and it does so more efficiently than the corresponding Cl and Br compounds. Thus, the E° values for the Tc (III)/Tc (II) reductions in DMF are -0.001, 0.103 and 0.372 volts versus the Ag-AgCl electrode for the Cl, Br and NCS complexes respectively. This explains why the Tc (II) isothiocyanato complex is stable in air, and can be further reduced to the Tc (I) complex, unlike the Cl and Br complexes. The latter Tc (II) complexes are easily air-oxidized, and show no indication that they will form their Tc (I) analogues.

C. Nitrosyl Complexes

A green nitrosyl complex of Tc (II) - $\text{trans-}[\text{Tc}(\text{NH}_3)_4(\text{NO})(\text{H}_2\text{O})]\text{Cl}_3$ was prepared by the ceric oxidation in 2M HClO_4 of the corresponding pink Tc (I) complex which is described below. There is indirect evidence that the pK_a of the coordinated water is about 2. Only the chloride salt has been obtained as a solid. Apparently the amine ligands can be easily displaced in this compound.

A nitrosyl complex compound, $\text{Bu}_4\text{N}^+ [\text{Tc}(\text{NO})(\text{Br})_4]^-$, has been prepared by reacting $\text{TcO}_2 \cdot \text{XH}_2\text{O}$ with NO in 4M HBr .⁵³⁷ It is possible to use the bromo complex in the synthesis of the chloro- and thiocyanato complexes.

XI.

Technetium (I) Complexes

A. Nitrosyl Complexes

The compound which was initially reported as $[\text{Tc}(\text{NH}_4\text{OH})(\text{NH}_3)_4\text{H}_2\text{O}]\text{Cl}_2$ ⁴⁷⁴⁾ was shown to be $[\text{Tc}(\text{NO})(\text{NH}_3)_4\text{H}_2\text{O}]\text{Cl}_2$ ²¹³⁾. The charge on the cation is +2, but the interpretation of the Tc valence is that this is a Tc (I) complex and that the NO group can be treated as a linear $(\text{NO})^+$ component. The Tc (I) state was strongly stabilized by back donation of π electrons to the nitrosyl group. The compound, which is pink, has electronic absorption bands at 487, 358, 305, 283 and 233 nm. The pK_a of the H_2O group is 7.3, pointing again to the reduction of electron density in the technetium. The compound decomposes in alkaline solution. The amine groups are very difficult to aquate, even in acid solution.

The assignment of the +1 oxidation state to the technetium is largely a matter of choice, arising from the structure of the complex, the short Tc-NO distance, the long N-O bond distance, and the low IR frequency of the nitrosyl group (1680cm^{-1}).

Additional nitrosyl complexes have been prepared.⁵³⁸⁾ The previously synthesized $[\text{Tc}(\text{CNCMe}_3)_3]\text{Cl}$ or PF_6 ⁵³⁹⁾ was converted to the nitrate salt. This was then treated with concentrated HNO_3 in glacial acetic acid to yield $[\text{Tc}(\text{NO})(\text{NCCMe}_3)_3]^+$ as the PF_6 salt. Alternatively NOPF_6 was added to an acetonitrile solution of the hexakis isonitrilo compound.

The tetra-*n*-butylammonium salt, $\text{Bu}_4\text{N}(\text{Tc}(\text{NO})\text{Br})_3$, was prepared⁵³⁷⁾ and reacted in air-free methanol with *t*-butyl isocyanide. A 32% yield of $\text{Tc}(\text{NO})\text{Br}_2(\text{CNCMe}_3)_3$ was obtained. The crystal structure showed that the technetium was 6-coordinate, with the three isonitrile ligands meridional to one another. The two bromine atoms were trans to each other, and one of the isonitrile ligands was trans to the almost linear NO (hence NO^+) ligand. The Tc-N-O bond angle was almost linear and the Tc-NO bond length was 1.726 Å, quite close to the 1.72 Å distance reported by Armstrong and Taube.²¹³⁾ The N-O bond length was about 0.06 Å shorter than that reported by them, suggesting that π back-bonding was less important than in their case. The author points out that it is possible to formulate the complex as Tc (I) - NO^+ or as Tc (III) - NO; however, the latter demands a bent N-O bond in contrast to the linear NO^+ .

B. Organometallic Complexes

The dibenzenetechneium (I) complex of Tc-99 was prepared by Palm, Fischer and Baumgaertner using a direct synthesis^{540a)} rather than by the decay of the corresponding ⁹⁹Mo compound, which produced the Tc-99m cation.^{540b, 540c)} TcCl_4 was heated in a sealed system with aluminum powder and AlCl_3 in benzene at 130°C for 2 days. The product, presumably a salt of AlCl_4^- , was hydrolyzed first in methanol and then in cool water, and the complex cation was precipitated from water as the PF_6^- salt. The yield was only about 7%. After reprecipitation from acetone-ether it was characterized in several ways. The electronic absorption maximum was at 400 nm ($\log \epsilon \sim 2$), it melted

with decomposition at 250°C, it was stable in air, did not react with acids or bases, and it was diamagnetic. The IR spectrum was practically identical with that of the corresponding rhenium compound, with which it was isomorphous.

Fischer and Schmidt synthesized and characterized dicyclopentadienyl technetium hydride.⁵⁴¹ Cyclopentadienyl sodium was added to TcCl_4 in tetrahydrofuran at -50°C. The system was warmed to room temperature, NaBH_4 was added and the mixture was heated. The reaction produced $(\text{C}_5\text{H}_5)_2\text{TcH}$, which was characterized by mass spectroscopy and by NMR. The compound reacted with HCl in water to form the dihydrodicyclopentadienyl technetium (I) chloride. The cation could be precipitated by NaPF_6 . The chloride reacted with NaOH to regenerate the hydride compound.

Additional syntheses were carried out by Fischer and Schmidt.⁵⁴² They treated benzene or hexamethylbenzene with TcCl_4 in the presence of a mixture of Al and AlCl_3 , and finally precipitated the cations $[(\text{C}_6\text{H}_5)_2\text{Tc}^+ \text{ or } (\text{C}_6\text{Me}_6)_2\text{Tc}^+]$ with NaPF_6 . The compounds were reduced with LiAlH_4 in $(\text{MeOCH}_2)_2$ to yield $\text{C}_6\text{H}_5\text{TcC}_6\text{H}_5$ and $\text{C}_6\text{Me}_6\text{TcC}_6\text{Me}_6\text{H}$ respectively. They were yellow diamagnetic compounds.

It was noted that $\text{TcCl}_4 + \text{NaC}_5\text{H}_5$ in the presence of NaBH_4 yielded $\text{C}_5\text{H}_5\text{TcH}$.

C. Carbonyl Complexes

The carbonyl complexes of $\text{Tc}(\text{I})$ are mixed complexes. Syntheses of technetium carbonylhalides were performed by reacting technetium (O) carbonyl with chlorine or with bromine in CCl_4 .⁵⁴³ The reactions produced dimers directly or after heating. These dimers had the composition $[\text{Tc}(\text{CO})_2\text{X}]_2$. They could be converted to the monomer $[\text{Tc}(\text{CO})_3\text{X}]$ by treatment with CO at 1000 psi and at 100°C for 40 hours. In turn the pentacarbonyl halides could be converted to the dimers by heating in air at 100° for 24 hours.

The iodide was synthesized by reacting $\text{Tc}_2(\text{CO})_{10}$ directly with I_2 at 100° in sealed ampoules.

The halocarbonyls of $\text{Tc}(\text{I})$ have been useful as starting reagents for some organometallic complexes. Thus, Palm, Fischer and Baumgaertner reacted the chlorocarbonyl complex of technetium with cyclopentadienyl sodium to yield mostly $\text{C}_5\text{H}_5\text{Tc}(\text{CO})_3$.⁵⁴⁴ The compound melted at 87.5°. It had an absorption maximum at 274 nm ($\log \epsilon = 3.69$). In turn this complex was reacted with benzoyl chloride in the presence of AlCl_3 to yield $\text{C}_6\text{H}_5\text{COC}_5\text{H}_4\text{Tc}(\text{CO})_3$.⁵⁴⁵ The compound was purified by sublimation in a high vacuum.

Kaden et al prepared a variety of $\text{Tc}(\text{I})$ mixed carbonyl complexes by reacting $\text{Tc}(\text{CO})_3\text{Br}$ with various ligands.⁵⁴⁶ Thus, the carbonyl bromide was refluxed in acetonitrile and on the addition of NH_4PF_6 , AgNO_3 , alcohol and water, a new compound was formed and then extracted with methylene chloride. It corresponded to $[\text{Tc}(\text{CO})_3(\text{CH}_3\text{CN})]\text{PF}_6$. It was characterized by its IR spectrum. Other ligands produced fac $[\text{Tc}(\text{CO})_3(\text{m-NaO}_2\text{SC}_6\text{H}_4\text{PPh}_2)_3]\text{PF}_6$, from the reaction between $\text{NaO}_2\text{SC}_6\text{H}_4\text{PPh}_2$ and the acetonitrile complex. With PPh_3 they obtained $[\text{Tc}(\text{CO})_3\text{CH}_3\text{CN}(\text{PPh}_3)_2]\text{PF}_6$ and with Me_2PhP_2 in CHCl_3 they reported $\text{Tc}(\text{CO})_3\text{Cl}(\text{Me}_2\text{PhP})_2$. The NMR spectra of the various complexes were measured in preparation for a broader investigation.⁵⁴⁷

Tsutsui et al had discovered that it was possible to insert metals into porphyrins by reacting the latter with metal carbonyls.⁵⁴⁸ With this technique they prepared a series of metalloporphyrin complexes of technetium (I).⁵⁴⁹ $\text{Tc}(\text{CO})_{10}$ was reacted with various porphyrin compounds in decalin at an elevated temperature. One such porphyrin was monohydrogen mesoporphyrin IX dimethyl esterato ($\text{H}_2\text{MPIXDME}$). Solids were isolated and analyzed and their structures were determined. They are $\text{Tc}(\text{I})$ compounds. Two metal atoms are bonded to the porphyrin, one above and one below the plane of the porphyrin. Each technetium is bonded to three nitrogen atoms and to three carbon monoxide molecules. In these bimetallic compounds the porphyrin behave like a hexadentate ligand.

It is also possible to prepare monometallic compounds in which the porphyrin behaves like a tridentate ligand.

Tc(I) carbonyl-containing complexes could be prepared by reacting Tc(III) phosphine complexes with carbon monoxide.⁵¹⁴ The Tc(III) complexes $(\text{Tc X}_2 (\text{P}(\text{OEt})_2\text{Ph})_2)\text{Y}$ in which $\text{X} = \text{Cl, Br or I}$, and Y is Cl^- , I^- , BPh_4^- and ClO_4^- , were prepared by reacting $(\text{NH}_4)_2\text{TcX}_6$ with excess diethyl phenyl phosphonite in ethanol. Ethanol solutions of these complexes take up CO in the order $\text{Cl} < \text{Br} < \text{I}$. Both *cis* and *trans* isomers are formed, in the ratio 40:60. A *cis* isomer - $[\text{Tc}(\text{CO})_2\text{L}_2]^+ \text{ClO}_4^-$ was studied crystallographically. The structure has discrete monomeric octahedral cations of *cis*- $[\text{Tc}(\text{CO})_2(\text{P}(\text{OEt})_2\text{Ph})_2]^+$ with some distortion.

Similar syntheses of mixed carbonyl-phosphine complexes by reaction of Tc(III) phosphine compounds with carbon monoxide have been carried out.⁵⁵⁰ The voltametric behavior of $\text{Tc Cl}(\text{CO})_2(\text{PMe}_2\text{Ph})_2$ and of $\text{TcCl}(\text{CO})_2(\text{PMe}_2\text{Ph})_2$ was studied in acetonitrile.⁵⁵¹ Both compounds undergo a 2-electron oxidation (forming Tc(III) complexes).

Pseudo-allyl ligands like the triazenido group were incorporated in phosphine-carbon monoxide-chloride complexes of Tc(I) by displacing the halogen.⁵⁵² The intermediate compounds - $\text{Tc}(\text{PMe}_2\text{Ph})_2(\text{CO})_2\text{Cl}$ and $\text{Tc}(\text{PPh}_3)_2(\text{CO})_2\text{Cl}$ - were added to a mixture of a dried hexane solution of *n*-butyllithium and a dried benzene solution of Ar NHX Ar under nitrogen, and refluxed for three hours, (Ar is an aromatic residue - C_6H_5 or $\text{CH}_2\text{C}_6\text{H}_4$, or pClC_6H_4 ; $\text{X} = \text{N}$, or $\text{C}(\text{CH}_3)_2$) forming $[\text{Tc}(\text{PMe}_2\text{Ph})_2(\text{CO})_2(\text{p-CH}_3\text{C}_6\text{H}_4\text{N} \cdots \text{N} \cdots \text{NC}_6\text{H}_4\text{CH}_3)]$ and $[\text{Tc}(\text{PMe}_2\text{Ph})_2(\text{CO})_2(\text{C}_6\text{H}_5\text{N} \cdots \text{C}(\text{CH}_3)_2 \cdots \text{NC}_6\text{H}_5)]$. The addition of ethanol produced a yellow solid which was analyzed by X-ray diffraction after recrystallization. The structure showed two *cis*-CO groups, two axial PMe_2Ph groups and the chelate ligand which formed a 4-membered ring with the metal. The ligands were coordinated in bidentate fashion. There was some deformation from an octahedral structure caused by the small bite of the ligands.

The authors believed that there was complete delocalization of the π systems of the two anions.

D. Hexacyano Complexes

A hexacyanotechnetate(I) salt was prepared by Herr and Schwochau (loc cit) and investigated in more detail.⁵⁵³ It was prepared by reducing either a pertechnetate salt or a $[\text{Tc}(\text{OH})_3(\text{CN})_4]^{2-}$ salt with potassium amalgam in the presence of KCN. An olive-green solid was obtained. Its formula was deduced from that of the Re species^{554a} because of the similarities in the electronic spectra of the two salts. In addition, the infrared spectra of $\text{K}_3\text{Tc}(\text{CN})_6$ and of $\text{K}_3\text{Re}(\text{CN})_6$ were virtually identical. Finally, the X-ray diffraction patterns of the technetium complex, of $\text{K}_3\text{Re}(\text{CN})_6$ and $\text{K}_3\text{Mn}(\text{CN})_6$ were superimposable.

The technetium complex, like the other two, has a rare gas electronic configuration. Nevertheless, it is oxidized in air. Higher-valent technetium cyanide complexes are formed.

E. Isonitriles

The first reported isonitrile complex of technetium was the hexakis (tert-butyl isocyanide) technetium(I) hexafluorophosphate, which was synthesized from hexakis (thiourea-S) technetium(III) chloride by reaction with tert-butylisocyanide in methanol under reflux.^{554b} A later synthesis of isonitrile complexes was based on the reduction of pertechnetate-99 by alkaline sodium dithionite in the presence of the ligand in an ethanol-water mixture.^{554c} This facile synthesis of Tc(I) complexes from pertechnetate was extended to the tert-butyl, methyl, cyclohexyl and phenyl isocyanide compounds. All (as the hexafluorophosphates) were characterized by elemental analysis, electronic, infrared and proton magnetic resonance, conductance, cyclic voltametry and field desorption mass spectrometry. The various compounds were stable in air and water, were soluble in polar organic

solvents, and showed the conductance expected of 1:1 electrolytes in acetonitrile solution. The alkyl complexes exhibited a reversible 1-electron oxidation at 0.82-0.88 V vs. SCE in acetonitrile. That of the aryl complex was at 1.18 V vs. SCE. The direct synthesis from pertechnetate also made it possible to prepare the complexes at the 10^{-8} - 10^{-9} M level with ^{99m}Tc .

Another method of synthesis of the hexakis isonitrile complexes of Tc(I) was reported by Kennedy and Pinkerton.^{554d} This involved the prior synthesis by electrolytic or chemical reduction of formate, acetate or pivalate complexes of technetium, whose oxidized form was reacted with the hexakis isocyanide reagents.

The Tc(I) oxidation state is achieved with isonitriles because of the nature of the ligand. In the formal sense, the carbon atoms are divalent. This makes it possible for the lone electron pair to form a σ -type donor bond to metal ions. If the metal ion has filled d-orbitals which can overlap with low, empty, antibonding orbitals of the attached ligand atom, a π type bond may also form. Such a back-donating bond can reduce the negative charge on the metal which had been produced by the donor bond. Back donation increases as the positive charge on the complex decreases. In this sense, isocyanides will behave like carbon monoxide, in that low oxidation states of metals will be stabilized.^{554e}

F. Other Complexes of Tc (I) and Tc (II)

When S_2Cl_2 in CH_2Cl_2 was reacted with dichloro (nitrido) tris (dimethylphenylphosphine) technetium (V), thionitrosyl complexes of Tc (I) and Tc (II) were obtained.⁵⁵⁵ At room temperature, with stoichiometric proportions of S_2Cl_2 and the nitrido complex, the Tc (I) complex is formed: $\text{Tc}(\text{NS})\text{Cl}_2(\text{Me}_2\text{PhP})_3$. If SnCl_4 is in excess and the mixture is refluxed, the main product is the Tc (II) complex: $\text{Tc}(\text{NS})\text{Cl}(\text{Me}_2\text{PhP})_3$. The N-S stretch is quite strong in both the Tc-I and Tc-II compounds, at 1177cm^{-1} for Tc (I) and at 1240cm^{-1} for Tc (II). The Tc (I) complex melts at $141\text{-}143^\circ\text{C}$, the other at $144\text{-}149^\circ$.

XII.

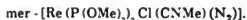
Complexes of Tc(0)

A. Ditechnetium Decacarbonyl Complexes

The main (and perhaps the only) Tc(O) complex is $\text{Tc}_2(\text{CO})_{10}$, ditechnetium decacarbonyl. It was prepared by heating Tc_2O_7 in CO at 250 atmospheres at 275°C for 12 hours⁽⁵⁵⁶⁾ or at 220° and 3000 lbs/in² CO pressure for 20 hours.⁽⁵⁵⁷⁾ It can be purified by sublimation, yielding colorless crystals which melt at 159°-160°C. It decomposes slowly in air. It was characterized initially by its IR spectrum, which showed three distinct carbonyl bonds. Its crystal structure showed that it was isomorphous with $\text{Mn}_2(\text{CO})_{10}$ and $\text{Re}_2(\text{CO})_{10}$.⁽⁵⁵⁸⁾ In the solid each metal atom is octahedrally coordinated to 5 carbonyl groups and to the other metal atom. The equatorial carbons are in a staggered configuration.

B. Technetium Dinitrogen Complexes

Technetium dinitrogen complexes were prepared by the reduction of $\text{TcCl}_4(\text{PPh}_3)_2$.⁽⁵⁵⁹⁾ The parent complex was treated with 2% sodium amalgam in benzene under nitrogen, with the addition of 1,2-bis diphenylphosphinoethane. After ten hours the new complex was crystallized from benzene. The yellow-brown crystals dissolved readily in benzene and toluene, but poorly in hexane and ethanol. The complex was $\text{Tc N}_2(\text{diphos})_2$. The authors believe that it has a $\text{Tc-N} \equiv \text{N}$ bond with linear coordination, from its infrared spectrum. The technetium is 5-coordinate. The Tc oxidation state may be zero, because some corresponding Re (I) complexes have no electrical charge if there is one Cl in the complex.



The oxidation state of the technetium is undoubtedly low. This is probably due to the π -accepting ability of the N_2 moiety.⁽⁵⁶⁰⁾ That is, $\text{M-N} \equiv \text{N}$ is very much like $\text{M-C} \equiv \text{O}$.

XIII.

Tc-99m Radiopharmaceutical Preparations

There are hundreds of articles in the literature which deal with Tc-99m radiopharmaceutical preparations. They are too numerous to analyze and to discuss. This section will be limited to several topics of chemical interest: some general considerations about all Tc-99m preparations, several methods of determining some feature of technetium chemistry at the tracer level, and a discussion of labeling proteins-albumin, antibodies, etc.-with Tc-99m.

A. General Considerations

The chemistry of Tc-99m radiopharmaceuticals is one of extremely dilute solutions. It is complicated by the inevitable presence of Tc-99 so that the total concentration of technetium in the sample will depend on the previous history of the generator. This total concentration, if sufficiently high, may have an adverse effect on some subsequent reductions because about 13% of the Mo-99 will decay directly to the long-lived Tc-99. The latter is also produced, of course, by the decay of Tc-99m. Theoretical calculations have taken both sources into account.⁽⁵⁴¹⁻⁵⁴³⁾ Two experimental determinations of total technetium in generator milkings have been reported. One is based on technetium yields from generator eluates, determined by liquid scintillation counting.⁽⁵⁴⁴⁾ The second rests on the determination, by UV absorption of pertechnetate isolated by anion-exchange HPLC.⁽⁵⁴⁵⁾ The latter, analyzing the output of a 7,450 mCi generator at various intervals, showed that the total concentration of technetium ranged from $(1 \text{ to } 47) \times 10^{-7} \text{ M}$, or $(3 \text{ to } 35) \times 10^{-12}$ moles of total technetium per mCi of Tc-99m. The liquid-liquid extraction of instant technetium showed somewhat higher values: $(2 \text{ to } 178) \times 10^{-7} \text{ M}$, and $(20 \text{ to } 717) \times 10^{-12}$ moles of total Tc per mCi of Tc-99m. In both cases, the experimentally determined values are higher by about 35% than the calculated values. This means that the total concentration of technetium will extend from $3 \times 10^{-9} \text{ M}$ to about $3.5 \times 10^{-8} \text{ M}$ for 1 mCi of Tc-99m in one ml. of solution. For more active solutions, the total concentration of technetium will range from 10^{-8} M to 10^{-7} M .

There are a number of consequences arising from these estimates of the total concentration of technetium in radiopharmaceutical kits. In preparations in which the concentration of SnCl_2 as reductant must be limited, the total concentration of technetium may be too high for complete reaction with the tin. There are two cases: the *in vitro* labeling of red blood cells by SnCl_2 ,⁽⁵⁴⁶⁾ and the Ceretec kit.⁽⁵⁴⁷⁾ In these cases the tin concentration may be of the order of 10^{-7} M to 10^{-6} M . For the usual run of well-practiced Tc-99m radiopharmaceuticals, the concentration of tin salt is about 10^{-4} M - 10^{-3} M , and this should be more than sufficient.

A second problem which may arise from variable total pertechnetate concentrations has been called the availability of tin.⁽⁵⁴⁸⁾ This does not appear if the reductant has been prepared by dissolving SnCl_2 in HCl, diluting to an appropriate concentration, and using it directly. Occasionally in kits in which the SnCl_2 solution has been lyophilized, specimens have a much smaller concentration of Sn(II) than would be expected from the original formulation. The suggested criterion for the evaluation of

kits in this regard is the titration of pertechnetate-99 in the presence of DTPA by the reconstituted kit. The assumption in the analysis is that ^{99}Tc (III) represents the final oxidation state of the technetium.⁽²⁵²⁾ Actually, in the direct titration with SnCl_2 , the final oxidation state of technetium is 3.5.⁽²⁵²⁾ In the tests by titration, a number of commercial kits showed quite small quantities of available Sn(II) - very much less than what had been incorporated in the kit. The effect is probably due to the promotion of colloidal tin oxide as the lyophilized solutions become quite concentrated before solidification. At present there are no known methods of controlling the loss of available tin.

A third problem which may be posed by variable total concentrations of pertechnetate is interference in the kinetics of the reduction and substitution reactions. This is a complicated matter which involves largely unknown reaction mechanisms. In two instances, a decision is easy to make. The reduction of 10^{-4}M pertechnetate by excess SnCl_2 in the presence of 1M citrate takes place in two steps.⁽²⁵²⁾ The first step, producing Tc(V) , is rapid. The second step of the reaction would be so slow at 10^{-8}M or 10^{-9}M TcO_4^- that it can be ignored, regardless of the fairly large variations in the total technetium concentration in radiopharmaceuticals. Similarly, the reduction of 10^{-4}M pertechnetate by excess SnCl_2 in 0.2M pyrophosphate solution involves a slow step which was interpreted as a dimerization reaction following the initial rapid reduction to Tc(III) .⁽⁴²³⁾ This slow step, whose rate is governed by the square of the technetium concentration, requires many hours for completion at the 10^{-4}M technetium concentration. Hence it could be ignored at the radiopharmaceutical concentration level, regardless of wide variations in the technetium concentration.

It has been proposed more formally that the effect of varying total concentrations of pertechnetate can be interpreted in terms of the kinetics of first-order and second-order reactions with respect to the pertechnetate concentration.⁽⁵⁸⁶⁾ In reactions in which all reagents relative to pertechnetate are in very large excess, and in which a single pertechnetate anion is involved in the rate-determining step, the reaction will be pseudo-first order, independent of the technetium concentration. There is no quantitative study yet available for this situation.

In reactions in which the rate-determining step involves two technetium moieties, the time required for complex reactions is inversely proportional to the initial concentration of pertechnetate:

$$\frac{-d(\text{Tc})}{dt} = k(\text{Tc})^2 \quad \frac{1}{a-x} - \frac{1}{a} = \frac{x}{a(a-x)} = kt$$

Here "a" is the initial concentration of the pertechnetate, (a-x) is its concentration after time t, and x is the concentration of the reacted technetium.

$$t = \frac{1}{k} \times \frac{x}{a(a-x)} \quad \text{For virtually complete reaction, let } \frac{x}{a-x} = \frac{99}{1} \approx 100.$$

$$\text{Then } t = \frac{1}{k} \times \frac{100}{a}$$

The time required for virtually complete reaction (99%), is inversely proportional to the initial concentration of pertechnetate. At the present time, there is little knowledge of the velocity constants of dimerization reactions of technetium. The system which has been most studied is the disproportionation of technetate (TcO_4^{2-} , Tc(VI)) in neutral^(50, 231) or alkaline^(230, 231) solution. The constants are approximately 10^7 ,⁽⁵⁰⁾ or 10^{10} ⁽²³¹⁾ in neutral solution, or 10^3 in dilute alkali.⁽²³¹⁾ The diffusion-limited constant (for a reaction in which every collision is successful) is of the order of 10^{10} per mole-second. In such a case, whether the initial technetium concentration is 10^{-6}M or 10^{-9}M makes no practical difference. The reaction is over in much less than a second. However, if the velocity constant of the rate-determining step is 10^7 , a decrease in technetium concentration from 10^{-6}M to 10^{-9}M will mean that the requirement for complete reaction rise from about 1,000 seconds to

10,000 seconds. If the velocity constant is 10^5 , the dimerization reaction will be impossibly slow regardless of the initial technetium concentration.

The discussion has assumed that the reactions are homogenous, that the rate-determining steps are known, and that there are no complications. There is one known system which is not described by these simple expectations. The reduction of 10^{-4} M pertechnetate by concentrated HCl yields Tc (V) (as TcOCl_2^- or TcOCl_2^{2-}). Tc (IV) as $\text{Tc}(\text{Cl})_3^{2-}$ is produced only after long heating.³⁵¹ There is now general agreement with Shukla's finding that in the reaction of concentrated HCl with no-carrier added pertechnetate-99m, Tc (IV) is produced rather quickly, apparently by way of Tc (V), but that little or no Tc(V) remains.⁵⁶⁴ This follows earlier work by Williams and Deegan⁵⁶⁵ and by Munze and Noll⁵⁶⁶ who reported that $^{99\text{m}}\text{Tc}(\text{IV})$ was formed directly from TcO_4^- . It is possible that traces of iron may be responsible for this effect,⁵⁶⁷ but no detailed study has been made.

Other types of kinetic complications may be present in several standard kit preparations. While there have been no detailed kinetic studies of the formation of the $^{99\text{Tc}}$ -DTPA complex, a potentiometric titration of pertechnetate-99 with SnCl_2 in DTPA solution strongly suggested that a Tc(IV), (III) dimer was formed,⁵²² and Linder has most definitely shown this to be the case.⁵⁴⁴ The question which arises is whether the clinical preparation at the 10^{-6} M level of Tc concentration is also a dimer. If so, this would mean that the appropriate velocity constant would have to be not much less than $10^{15} \text{M}^{-1} \text{s}^{-1}$ since the clinical preparations are made ready in a short time. Alternatively, if the dimerization rate is slow, one must ask first what ligand or ligands complete the coordination of the technetium in the monomeric complex; secondly, whether a better ligand could be found which would render the complex more stable. A similar problem must arise in antibody labeling in which DTPA is covalently bonded to the protein, and Tc-99m is then complexed at that site.⁵⁶⁸ It is almost certainly out of the question for two antibody fragments, each with a technetium atom bonded to its DTPA, to come together to form a Tc-O-Tc dimer.

Another possible dilute system which at first glance may raise questions about the feasibility of dimerization and polymerization at very low levels of technetium concentration is the mysterious reduced hydrolyzed technetium.⁵⁶⁹ This is reduced pertechnetate which has escaped reaction with the ligand of the kit. It was originally described as "Technetium colloid" (presumably TcO_2) by Subramanian and McAfee in 1969 when they reported that sodium borohydride was useful in labeling various entities like proteins, DTPA, etc. with technetium.⁵⁷⁰ They found that the "colloid" did not pass through a 0.22 micron Millipore filter. A similar effect was reported by Lebowitz et al who tagged gelatin with pertechnetate reduced by NaBH_4 .⁵⁷¹ They found as much as 25% of the preparation was a radiocolloid. In the absence of gelatin, the technetium (presumably in the form of TcO_2) formed a colloid which was filtered out in the particular arrangement employed by them.

With the advent of stannous chloride as the reducing agent of choice in radiopharmaceutical quality control, experiments showed the presence of "reduced hydrolyzed technetium" in virtually every preparation; they are too numerous to enumerate. Thin-layer-chromatography and Sephadex column chromatographic techniques were used for its identification and measurement, but its nature was not clearly defined. It can be said that it is probably a mixed $\text{Sn}(\text{II})$ - TcO_2 colloid, since the earlier radiopharmaceutical literature described a stannous oxide colloid labeled with $^{99\text{m}}\text{Tc}$ which was useful in bone marrow imaging.⁵⁷² In addition, Sephadex gel chromatography with ^{115}Sn and $^{99\text{m}}\text{Tc}$ has shown a colloidal fraction containing both Sn and Tc.⁵⁷³ If SnCl_2 is used as the reducing agent, the appearance of the "reduced hydrolyzed technetium" most probably indicates a mixed SnO - TcO_2 colloid. One need not be concerned about the kinetics of polymerization of 10^{-6} M solutions of $^{99\text{m}}\text{Tc}$ in such cases.

However, in the case of reduction of pertechnetate-99m by sodium borohydride the presence of reduced technetium of colloidal size is more difficult to explain. The reference is to a radiopharmaceutical preparation which was called $^{99\text{m}}\text{Tc}$ -technetium dioxide for Liver Scanning.⁵⁷⁴ A colloid was formed by reducing $^{99\text{m}}\text{TcO}_4^-$ with NaBH_4 in acid solution without a carrier metal,

stabilizer, or anything but the generator eluate in saline. The technetium was in clear colorless solution, and 85% of the activity was deposited in the liver, suggesting most strongly that it was colloidal. The question is: does this preparation represent the polymerization of technetium in solution at a concentration much lower than 10^{-8}M ? The authors show an electron microscope study of a small sample. The particle size of the spherical particles was from 0.5 to 1 micron in diameter. The particles were quite uniform in shape and size. However, calculation showed that they could not be composed of technetium alone. The original solution contained 1mCi of pertechnetate in 25 ml of eluate. Generally, one takes from 1 to 10 μl of solution for electron microscope pictures (we assume 10 μl). There were about 80 spherical particles in the picture. Assuming that half were 1 micron in diameter and the remainder 1/2 micron, the combined volumes came out to $2.65 \times 10^{-11}\text{ cc}$ or, for TcO_2 , a mass of about $1.6 \times 10^{-10}\text{ grams}$. This meant that in 25cc there would be $4 \times 10^{-7}\text{ grams}$ of TcO_2 , whereas 1mCi of $^{99\text{m}}\text{TcO}_2$ would weigh about $2.5 \times 10^{-11}\text{ grams}$. Even if it is assumed that there is a tenfold enrichment of the technetium content by decay to ^{99}Tc , it is clear that while the particles in the picture contain technetium, they consist mainly of something else.

The authors state that reacting NaBH_4 with HCl under the same condition of concentration but in the absence of pertechnetate does not yield the same spherical particles in the electron microscope picture. One can conclude that the particles in question are to be found in the 2.5 ml of eluate from a technetium generator. At the time of publication of the article -1970- the usual source of ^{99}Mo was neutron bombarded molybdenum metal, rather than the fission product in widespread use today. This means that molybdenum (largely inactive) and perhaps aluminum are the major impurities to be expected in the eluate: the molybdenum as MoO_3 or $\text{Mo}_2\text{O}_4^{6-}$ polymer³⁵¹ and the aluminum as dimerized or polymerized aquo-ions from the activated alumina column, in addition to a heteropoly aluminomolybdate.³⁷⁶ The MoO_3 by itself will not form a colloid, since its room temperature solubility in water is about 1.0 g/liter.³⁷⁷ If it is assumed that the particles in the electron microscope picture are spheres of MoO_3 there will be about 10^{-10} grams in (assumed) 10 μl of solution, and $2.5 \times 10^{-7}\text{ grams}$ in the 25 ml of generator eluate. In the form of MoO_3 or its polymer, this would be soluble, and not colloidal (assuming that a colloid will form as a preliminary stage in the precipitation of an insoluble solid). However, there is another possibility. This is the combined action of pertechnetate and sodium borohydride, with or without complexing by aluminum. The borohydride can reduce both the pertechnetate and the molybdic oxide (or its polymer). One forms a molybdate blue. In this type of compound, the oxidation state of this molybdenum is between +5 and +6. Once formed, it is almost certainly colloidal.³⁷⁸ Schirmer et al prepared a molybdenum blue by reducing molybdate, and conducted both x-ray diffraction and electron photomicrographs. It was colloidal, with fairly uniform spherical particles which were 100 $\text{\AA}$ in diameter, together with some which were several times larger. This preparation has been known to be colloidal even in very dilute solution. While there are no reports of technetium-molybdate heteropoly compounds or blues, there is no lack of references for rhenium-molybdate or rhenium-tungstate reduced systems.^{379a-d} In short a heteropoly complex of technetium and molybdate is formed (with the possible inclusion of aluminum in the complex) and on reduction a molybdenum blue colloid is formed, carrying the technetium. In this case, too, there is no need to be concerned about the kinetics of polymerization of the technetium.

B. Methods of Chemical Characterization of $^{99\text{m}}\text{Tc}$ Complexes

The principal problem in the identification of the chemical nature of radiopharmaceutical preparation of $\text{Tc-}^{99\text{m}}$ is finding a means of identifying such properties as oxidation state, formation constant, molecular structure, electrical charge, etc. In this discussion we are ignoring dried solid samples of $^{99\text{m}}\text{Tc}$ compounds which have been examined by various methods, and examining radiopharmaceutical solutions as such. In general, workers in the field have directly determined some property or properties of technetium complexes at much higher technetium-99 concentrations (usually 10^{-4} - 10^{-3}M) and then compared this property with that shown at the 10^{-8}M level. If the two measurements were in agreement, it was concluded that the identity of the $^{99\text{m}}\text{Tc}$ compound was established.

The following procedures have been used in this way: polarography, various kinds of chromatography, ion-exchange, solvent extraction and electrophoresis.

1. Polarography and Coulometry

Relatively little work has been done with radiopharmaceutical solutions. The examination of such dilute solutions for a specific compound offers great difficulties. Heineman and his collaborators described the procedure for the measurement of $2.4 \times 10^{-10} \text{ M KTeO}_4$ in a phosphate buffer.⁵⁴⁰ It was necessary to lower the oxygen concentration to undetectable limits in order to exclude interference with the pertechnetate wave. The solution was boiled for an hour and argon gas was passed through it and over it; metal tubing was used in place of plastic tubing. All varieties of plastics are permeable to air to some extent.

At the 10^{-4} M level, pertechnetate in acid solution shows two irreversible waves. The first - a 4 electron reaction - has been extensively studied.^{541a-d} There is a general measure of agreement about it. The second wave - a 3-electron wave - is less well understood, largely because of interference by a catalytic hydrogen-discharge wave. The behavior of a very dilute pertechnetate solution - 10^{-10} M - has been examined by a technique called radiopolarography, introduced by Love and Greendale.⁵⁴² By means of this technique, one can collect mercury drops containing a deposited metal, an amalgam or a precipitate as a function of the applied voltage. Grassi et al used this technique on a 10^{-10} M solution of pertechnetate in acid.⁵⁴³ The half-wave potential of the second step was -0.904 volts versus saturated calomel on more concentrated ($2.95 \times 10^{-4} \text{ M TcO}_4^-$) solution at pH 2.83. With the radiopolarogram technique, the half-wave potential was -0.858 volts vs. saturated calomel in the pH interval 1 to 3. This is only slightly lower (by 36 mv) than the potential of the more concentrated solution.

Russell studied the polarographic reduction of $8 \times 10^{-4} \text{ M TcO}_4^-$ in EDTA solution with a variety of electrodes and in solutions of different pH.⁵⁴⁴ He then applied the potentials to $^{99\text{m}}\text{TcO}_4^-$ in the presence of EDTA in order to produce the complex coulometrically. In $1 \text{ M NH}_4\text{OH}$ and $0.1 \text{ M Na}_2\text{EDTA}$ the electrode potential was changed by 0.05 volts every half hour. The yield of electrolyzed Tc (presumably as the EDTA complex) was determined by chromatography on silica gel on glass fibers with an appropriate solvent. The potential at which reduction started in the tracer experiment was two to three hundred millivolts more negative than in the carrier experiment. The difference could not be accounted for by the time required to produce measurable products in the tracer experiment.

2. Chromatography

Chromatography has been the most widely used technique for the characterization of $^{99\text{m}}\text{Tc}$ complexes as well as for quality control of radiopharmaceutical kits. There are many examples of different varieties of chromatography in the nuclear medicine literature from mouse chromatography (that is, using distribution *in vivo*) to various two-dimensional systems on different supports with solvents ranging from aqueous saline solution to three-component systems. Column chromatography with Sephadex or Sepharose beads has also been used but all these - at least the ones on a non-instrumental level - suffer from lack of differentiation of closely related substances. They lack resolving power. Such resolution is offered by HPLC - high performance (or high pressure) - liquid chromatography. While it (like the other techniques) has been used extensively for quality control of kit preparation, it has been used infrequently for the comparison of the elution behavior of the known more concentrated Tc-99 complexes with that of the corresponding radiopharmaceutical. That is, the retention times of the two solutions of much different concentrations are compared.

3. Ion-exchange Chromatography

This technique, which was originally developed by Shubert⁽⁴⁰³⁾ and later by Fronaeus⁽⁴⁰⁴⁾, was introduced into radiopharmaceutical chemistry by Owunwanne, Marinsky and Blau.^(303, 304) The net charge on an ion or complex ion is determined by equilibrating the trace chemical between an ion-exchange resin and different concentrations of a much more concentrated solution of an indifferent electrolyte. This measurement yields the distribution of the radioactive tracer - the ratio of activity in 1 gram of dry resin relative to the activity in 1 gram of each of the different solutions. A plot of the log of the distribution against the log of the concentration of the indifferent electrolyte should yield a straight line whose slope is the ratio of trace ion charge to indifferent electrolyte (anion or cation) charge. Russell extended the method to a flow system, preferring that to the batch equilibration.⁽³⁸⁵⁾

The batch equilibration work showed that with cation-exchange, the product of the reaction of $^{99m}\text{TcO}_4^-$ with SnCl_2 in HClO_4 solution in the pH interval 1-2.5 had a charge equal to that of Sn^{2+} on the resin. For Tc-99m-HEDP on an anion-exchange resin there were two components with charges -2 and -0.5. The work on the cation-exchange resin was discussed earlier. There are two exceptions which might be taken. The positively charged Tc-99m particle (tentatively identified by the authors as TcO^{2+}) may be colloidal or partly colloidal. The presence or absence of such a condition can be demonstrated by changing the ratio of resin mass to solution mass, as Schubert has shown.⁽⁴⁰³⁾ This point is raised because Munze and his collaborators⁽³⁷⁷⁾ had concluded that in the solutions described by Gorski and Koch⁽³⁷⁶⁾ there was colloidal TcO_2 , and one did not see truly ionic (cationic) technetium in solutions of HClO_4 more dilute than 1M.

A second exception to the reported work has to do with the behavior of anion-exchange resins of the strong base (quaternary ammonium) type. If there are several chemically related varieties of anion in solution - e.g., CoCl_3^{-1} and CoCl_4^{2-} , the resin may preferentially pick up one which was a minor component in the solution. This has been illustrated in an earlier section. Whether it applies to Russell's flow technique is not known, since he used DEAE cellulose, which has not been studied in a fundamental sense like the Dowex-1 type of resin, in spite of the very large number of separations reported with it.

One additional point concerns the behavior of the strong-base anion exchange resins with respect to polyvalent anions. Reference was made earlier to a Dionex advertisement which shows the order of elution of aqueous electrolyte solutions on a Dionex column (which is of the strong base type). The order is: $\text{Cl}^{1-} > \text{Br}^{1-} > \text{I}^{1-} > \text{SO}_4^{2-}$. This has been taken by various investigators as proof that the more highly charged anions are more firmly held by the resin than the various monovalent anion. The advertisement refers to the analysis of very dilute solutions. In an early paper which described the properties of Dowex-1 and Dowex-2, Wheaton and Bauman showed that in more dilute solutions of sulfate and chloride, the sulfate displaced chloride from the Dowex-2 resin.⁽³⁴⁶⁾ Conversely, when the electrolyte concentration exceeded 0.1M, the chloride displaced sulfate from the resin. At a sulfate concentration of 0.09M, the selectivities were the same for the two ions. Similar effects were seen in chloride-carbonate equilibria on the resin. This may present a complication if a comparison of concentrated Tc-99 and dilute Tc-99m complexes of high charge is made on anion-exchange resins. A series of different concentrations of the Tc-99 complexes may have to be run.

With respect to the troublesome question of the importance of the charge on sulfate anions and their uptake by strongly basic anion-exchange resins, reference was made earlier to the fact that sulfuric acid was strongly taken up by Dowex-1 already in the sulfate form. The authors, who determined the activity coefficient of HSO_4^- in the resin phase, had concluded that HSO_4^- might well be a much weaker acid in the resin phase than in water.⁽⁴⁵³⁾ An indirect proof of this was found recently in titrations of sulfuric acid with Bu_4NOH solution in concentrated aqueous solution of quaternary ammonium salts like Bu_4NCl in approximately 3-3.5M solution. In water, the titration of sulfuric acid with a strong base shows a single end-point, in the vicinity of pH7, since HSO_4^- is a relatively strong acid ($\text{pK} = 2$). In the concentrated quaternary ammonium salt solutions, sulfuric acid

behaves like a mixture of HCl and acetic acid; there are two end-points. One is for the H_3O^+ of the first dissociation, and the second is for the HSO_4^- ion. It does behave like a weak acid in that medium, with an apparent pK of 4-5, depending on the salt and its concentration.⁽⁵⁸⁷⁾ By implication, it is a weaker acid in the resin.

4. Solvent Extraction

A method of determining the oxidation state of technetium in some radiopharmaceuticals is based on the formation by a substitution reaction of a well-defined neutral technetium complex which in turn is readily extracted by water-insoluble organic solvents.⁽⁵⁸⁸⁾ For a number of complexes which had been shown to be Tc(V) compounds at higher concentrations, the reagent is 8-hydroxyquinoline, symbol HOx, which forms a 1:1 dioxochelate whose composition is $\text{TcO}_2\text{Ox} \cdot 2\text{H}_2\text{O}$, like the corresponding Re(V) complex.⁽⁵⁸⁹⁾ When the Tc-99m chelate is formed, it is extracted into chloroform from a saturated Na_2SO_4 solution containing boric acid. The sodium sulfate salts out the oxinate complex, and the boric acid ties up cis polyhydroxy ligands like gluconate and mannitol. Under these conditions of extraction, it was found that the gluconate, mannitol and citrate complexes formed by SnCl_2 reduction in $2 \times 10^{-3}\text{M}$ pertechnetate solutions were extracted into chloroform-oxine solutions almost completely. It was concluded that the oxidation state of technetium in each case was the same as that determined by other means in 10^{-3} - 10^{-4}M pertechnetate solutions.

Tc-pyrophosphate, Tc-HEDP and Tc-DMSA formulations prepared with SnCl_2 showed practically no extraction with 8-hydroxyquinoline in chloroform. However, they were extracted into chloroform by 1, 5-diphenylcarbazone, whose oxidized form, the corresponding carbazide, reacts with pertechnetate itself to form a neutral carbazone complex of Tc(IV) of unknown composition.⁽⁵⁹⁰⁾ The carbazone is much less satisfactory as a Tc(IV) reagent than oxine is for Tc(V) compounds. Tc(IV) prepared by the reduction of TcO_4^- by concentrated HCl at 90°C reacted readily with the carbazone and gave variable but consistently high yields of extracted technetium. In the case of the pyrophosphate and HEDP preparations, it was necessary to demask them with a ferric salt, and to decompose the Tc complexes further with 1.5M HCl before extraction took place. The DMSA complex was broken with HCl and HgCl_2 . About 40% of the technetium was extracted in the latter case.

Oxidation of technetium by traces of air (which are inevitably present in any open system) was observed in solutions containing a ligand which could form a technetium complex in the higher (oxidized) state. Thus, Tc(IV) formed from concentrated HCl was not extracted by oxine in chloroform. However, when sodium gluconate was added to the Tc(IV) preparation, there was always subsequent extraction by oxine, the yield ranging from 20% to almost 100%. If SnCl_2 was added to the Tc(IV) solution and this was followed by the addition of gluconate, the oxine extraction was seriously decreased. The system - Tc(IV)-gluconate- O_2 - represents a coupled oxidation and complexation of technetium, involving traces of air and the added gluconate. This may turn out to be serious in the preparation of some technetium radiopharmaceuticals by ligand exchange. In one case, it was (mistakenly) claimed that the Tc-gluconate complex was a Tc(IV) compound⁽⁵⁹¹⁾ and it was shown that Tc-99m pyrophosphate exchanged with added gluconate.⁽⁵⁹¹⁾ This was taken as proof that the pyrophosphate complex was a Tc(IV) complex. When the oxine extraction was used on the system, it was found that the Tc pyrophosphate - not extractable by itself - became extractable after the addition of gluconate.⁽⁵⁸⁸⁾

The postulated induced oxidation and exchange is probably the reason for a well-known artifact in gel chromatography. The $^{99\text{m}}\text{Tc}$ -pyrophosphate kit preparations are strongly taken up by Sephadex columns, but not Biogel (polyamide) columns. The adsorption is minimized or eliminated by eluting the sample with a sodium pyrophosphate solution in place of the usual saline. The $^{99\text{m}}\text{Tc}$ -pyrophosphate is probably a Tc(III) or Tc(IV) compound. It is a weak complex, readily liberating Tc. The latter will encounter some of the many vicinal hydroxyl groups of the Sephadex and, in the presence of a little air, it will be oxidized and then complexed by vicinal OH groups of the Sephadex, which will hold the Tc(V) as it holds Tc(V) gluconate. The presence of sodium pyrophosphate in the

eluant will introduce competition between the OH groups and the added pyrophosphate for the liberated Tc particles.

It is possible that the finding by Johannsen of an exchange reaction between Tc-99m HEDP and o-phenylenediamine⁵⁹² is also due to a coupled oxygen oxidation and simultaneous or subsequent complexation, producing a Tc(V) amine complex from a lower-valent HEDP compound. His own explanation was that the exchange took place between the diamine and a ^{99m}Tc(V) - HEDP complex which was a different product from that obtained at higher technetium concentrations.

Another possible example of such induced oxidation and exchange reactions is in the formation of ^{99m}Tc(V)-cyclam from ^{99m}Tc-DTPA in alkaline solution.⁵⁹³ It was established conclusively that the ⁹⁹Tc-DTPA complex decomposed above pH 11, and that the decomposition of this complex in the alkaline solution preceded the formation of the ^{99m}Tc-cyclam complex. The latter is most certainly in the Tc(V) state. The authors considered two explanations: the DTPA complex decomposed with oxidation of the technetium to the (V) state, or the DTPA complex was initially in the V state. The latter possibility can be ruled out. ⁹⁹Tc(V) gluconate prepared without excess SnCl₂ shows no spectral change on addition of DTPA. If excess SnCl₂ is added to the last mixture, there is a spectral change, attributable to the formation of a lower-valent Tc complex. If the gluconate complex is prepared by NaBH₄ reduction of ^{99m}TcO₄⁻ (with the presumed elimination of excess reductant) it can be extracted into chloroform with oxine quantitatively. If DTPA is added to the solution before extraction, the high extraction efficiency is maintained. If SnCl₂ is now added to the Tc(V)-gluconate-DTPA mixture, there is a time-dependent decrease in the efficiency of extraction by the oxine which is attributed to the slow reduction of the Tc(V) gluconate to a lower oxidation state. If the ^{99m}Tc(V) gluconate without DTPA is treated with a large excess of SnCl₂ there is no decrease in the highly efficient extraction of the technetium by the oxine.⁵⁸⁴

It is reasonable to expect that the coupled dissociation-oxidation-complexation of technetium will take place with weak, easily dissociated complexes in lower oxidation states.

5. Electrophoresis

An investigative technique which has been applied directly to solutions of ^{99m}Tc compounds is based on a clever combination of synthesis and electrophoresis.^{594,595} Usually the electrophoresis of a Tc-99m compound is run on paper or on a cellulose derivative and its mobility is compared with that of a reference compound in the same medium (usually pertechnetate). In the technique under discussion, a ligand similar to the complexing agent is synthesized, but is given an additional group which is capable of bearing a charge, like a carboxylic acid or an amine. The added group must be located on the ligand molecule far from the functional entities which complex the technetium. The electrophoretic pattern of the technetium complex of this synthesized ligand is also run. One then looks for mixed ligand complexes in a ^{99m}Tc preparation made with ligands in solution. The electrophoretic pattern will then give information about both the composition of the original complex and its charge. If the complex is a 1:1 compound (technetium:ligand) there will be two bands or spots coming from the mixed ligand solution. One will be that of the original complex. The other will be that of the modified ligand which will now have a different charge from the original complex. If the complex is a 1:2 compound (technetium:ligand) there will be three bands or spots in the electrophoretic pattern. These will be the two original bands, and an intermediate band which will contain two ligands with different charges. Obviously, the ionizable group must be in its charged form for the differentiation to work. The method has been applied to technetium complexes of dihydrothioic acid to 1,2-dimercaptopropane and 1,3-dimercaptopropane, and to a number of HIDA types. The dimercapto compounds, like several of the HIDA types showed mixed-ligand formation with reduced technetium showing that there were two ligands per technetium. Smith and Byrne, who had synthesized and characterized the Tc-99 complex of dimercaptoethane,²⁴⁹ had shown by various techniques that there were two dimercapto ligands and one terminal oxo group bound to the

technetium, and had further shown by electrophoresis and chromatography that the ^{99}Tc complex was identical to the $^{99\text{m}}\text{Tc}$ preparation.⁵⁰⁶

In connection with the HIDA type of ligand, Burns et al not only showed that the ratio of ligand to technetium was 2:1, but that the $\text{HIDA-}^{57}\text{Co(III)}$ and the $\text{HIDA-}^{51}\text{Cr(III)}$ complexes showed the same electrophoretic behavior as the $^{99\text{m}}\text{Tc}$ complex. This strongly supported the conclusion that the $^{99\text{m}}\text{Tc}$ was in the Tc(III) state, which is in accord with the earlier finding by Loberg and Fields.¹³⁷¹

Similar work was carried out on the cyclam complex of technetium by Simon et al.³¹⁰ They established that the oxidation state of Tc-99 was +5, that its charge was +1 by reference to cyclam complexes of other transition metals, and that the electrophoretic behavior of the Tc-99m complex was the same as that of the Tc-99 compound.

C. Labeling Proteins with $^{99\text{m}}\text{Tc}$

A major difficulty in understanding the chemistry involved in labeling various proteins with $^{99\text{m}}\text{Tc}$ is that no metalloprotein containing ^{99}Tc has been prepared and characterized. Thus, it is not possible to establish at the millimolar or equivalent level the nature and number of the possible sites in the various proteins which can bind reduced technetium. Qualitative tests have shown that the following amino acids form weak complexes with $^{99}\text{TcO}_4^-$ treated with SnCl_2 : histidine, asparagine, serine and threonine as well as *N*-acetylglycinamide. Cysteine also forms a complex with reduced technetium, but it is probably much stronger than the other amino-acid complexes. None of the remaining common amino acids appear to form complexes.³⁹⁷ However, this is of limited importance since the structure and conformation of the protein complex are important and the assistance of nearest neighbors like peptide bonds may help to stabilize the primary binding of the technetium.

The labeling of albumin with $^{99\text{m}}\text{Tc}$ was first carried out successfully by McAfee et al in 1964.⁵⁹⁶ Their method involved the reduction of pertechnetate by FeCl_3 and ascorbic acid. In a modification, pertechnetate was first added to the reagents, the pH was raised to 9.0 or 9.5, the serum albumin was added, the pH was re-adjusted to 2, and after several minutes was raised to between 5 and 6.⁵⁹⁹ The method was quite successful. The chemistry was not obvious (see the section on reducing agents). Steigman et al operating on the hypothesis that the single sulfhydryl group of albumin was important in the formation of the complex effectively blocked it with either HgCl_2 which formed a very stable sulfhydryde complex or with *N*-ethylmaleimide (which alkylated the S-H group). The procedures practically eliminated the technetium binding to the protein. They also found that excellent yields of bound technetium could be obtained at pH 12, eliminating the acidification to pH 2.²²³

Hnatowich et al attempted to repeat this work by blocking the S-H group of albumin with HgCl_2 .⁶⁰⁰ The yield of labeled albumin was unaffected by the addition of HgCl_2 , but this may have been due to their use of SnCl_2 as the reducing agent rather than FeCl_3 -ascorbic acid. HgCl_2 is certain to react with the SnCl_2 ; this is the basis of the classical Zimmerman-Reinhardt procedure for analyzing specimens for their iron content.⁶⁰¹ A repetition of the original S-H blocking experiment with *N*-ethylmaleimide was carried out, using SnCl_2 as the reducing agent. It was found that there was no decrease in the yield of Tc -labeled albumin because of the blocking of the S-H group.²²⁴ This was also the case when FeSO_4 was used as the reducing agent.²²⁵

Albumin is unusual among proteins in a number of ways. There are complex rearrangements which take place in acid solution, and others in alkali. In acid there is marked expansion,⁶⁰² an increase in levorotation below pH 4,⁶⁰³ a marked increase in viscosity,⁶⁰⁴ a dimerization^{605 a, 6} and an isomerization.^{606 a-c} The isomerization which is called *N* $\rightarrow$ *F* reaction (*N* for native, *F* for fast-moving) shows itself in acid solution by heterogeneity in electrophoresis. The *F* component is faster-moving than the native structure, and probably represents not only a structural change, but also an increased proton attachment and, hence, an increased positive charge. In addition, at high pH UV spectra show

the unmasking of tyrosine groups which had been hidden by hydrophobic groups before the albumin unfolded.^{607 a, b)} Other normally hidden groups are also unmasked at high pH, including disulfides, thiol,⁶⁰⁸ and others. Work on the structure of albumin showed that the one S-H or cysteinyl group is residue #34 in a CNBr-formed, 88-residue fragment with a terminal aspartyl residue.⁶⁰⁹ There are 14 neutral, mainly hydrophobic residues before the S-H group. It is possible that the acid (or alkaline) step rearranges these groups so that the access to the S-H group is improved. It is also possible that supporting groups like histidine may occupy nearer positions to the S-H group and exhibit favorable geometries for the technetium. It is not out of the question for the acidification to permit a change in location of the S-H group by intramolecular exchange with a disulfide group and, thus, facilitate the formation of a technetium complex. Finally, it is possible that the S-H group not only complexes the technetium, but also makes possible the formation of the dimer^{605 a, b)} but blocking it prevents dimer formation.

Because three adjustments of pH were necessary in the iron-ascorbate labeling procedure, investigators turned to a 1-step, SnCl_2 addition to an albumin solution at acid pH.⁶¹⁰ This had the effect of obscuring the direct labeling of the albumin with reduced technetium in the sense that some of the technetium could have formed a mixed small colloid with stannous oxide which was stabilized or protected by a coating of albumin.⁶¹¹ Probably this was not the case in a sufficiently acid solution. In any event, it became the almost universal method of labeling proteins with $^{99\text{m}}\text{Tc}$, including fibrinogen, various enzymes, actual cells, etc. - preparations which are too numerous to list.

Labeling albumin with technetium appears to give different complexes with different reductants. An additional method which cannot be reconciled with the other two consists in the reduction of $^{99\text{m}}\text{TcO}_4^-$ with either dilute⁶¹² or concentrated⁶¹³ HCl evaporated to dryness. The Williams and Deagan paper reported that ascorbic acid added to the albumin mixed with the dried $^{99\text{m}}\text{Tc}$ deposit and brought to pH 2.5 gave a high yield of labeled albumin. Sundrehagen reported that binding of $^{99\text{m}}\text{Tc}$ to various proteins was poor with ascorbic acid, but excellent with gentisic acid. Albumin was not specifically mentioned.

With the advent of monoclonal antibodies, the various protein labeling procedures were examined more closely. While direct labeling is the simplest procedure, the resulting complexes - as Eckelman et al had pointed out⁶¹⁰ - were weak, tending towards instability. Paik et al suggested that the technetium is bound by both a high-capacity, low-affinity site, and a high-affinity, low-capacity site, and identified the latter with sulfhydryl groups produced by reduction of disulfide bonds.⁶¹⁴ Paik et al then suggested that all radiolabeling with $^{99\text{m}}\text{Tc}$ or with ^{111}In should be done in the presence of excess DTPA. While decreasing the radiochemical yield, this guarantees an inert chemical bond through the high affinity sites or through a bifunctional chelate.⁶¹⁵ They were able to transchelate technetium from low affinity to high affinity sites by raising pH to about 9 without any transfer from the antibody to DTPA in solution.

A second method of labeling antibodies (and other proteins) was by ligand exchange. Rhodes et al reduced pertechnetate - $^{99\text{m}}\text{Tc}$ with SnF_2 in acetic acid, and added the mixture to a Sephadex G-25 column, which retained the activity at the top. After washing it, they added the protein in citrate-dextrose, followed by elution with saline.⁶¹⁶ While it is possible that the protein was labeled with $^{99\text{m}}\text{Tc(IV)}$, it is more likely that a Tc(V) complex with the Sephadex was formed, perhaps with air oxidizing it to that state. Certainly one could anticipate that a Tc(V) citrate complex was formed in preliminary fashion. Unpublished experiments in which Tc(V) gluconate or Tc(V) citrate were formed with tin metal (leaving practically no excess of Sn(II)) showed that in acid solution both human serum albumin and IgG were labeled with 70% of the technetium added.⁵⁹⁷

Another method of labeling antibodies which was developed by Rhodes et al was the pre-tinning of the antibody with SnCl_2 for up to 21 hours at room temperature. The pertechnetate was then added, in the absence of air.⁶¹⁷ They report that F(ab')_2 was in part broken into F(ab') monomer fragments

which were labeled more than $F(ab')_2$. They thought that the prolonged pretinning of the antibody reduced some disulfide bonds to S-H groups which then coordinated the reduced technetium.

Another method of labeling antibodies with Tc-99m consisted of the prior preparation of a bifunctional chelate of Tc-DTPA.^{618 a, b} The DTPA is considered a bifunctional chelate in that it binds to the protein (by a condensation reaction of cyclic acid anhydride with lysine amino groups) and to the ^{99m}Tc . The problem with DTPA-attached antibodies is that some fraction of reduced pertechnetate -99m binds elsewhere on the protein.⁶¹⁴ In passing, Lantaigne and Hnatowich suggested that the site of binding of technetium to proteins is the helical portion of the macromolecule.^{618 a} There is no evidence to support this hypothesis, and there is no chemical reason for it. One way of reducing the fraction of direct binding is to include free DTPA in the labeling solution. This lowers the extent of direct binding, but also seriously decreases the total yield of labeled protein.^{614, 615}

Other bifunctional approaches include: derivatives of dimercaptoacetamide (DADS),⁶¹⁹ derivatives of bis-N-methylthiosemicarbazone⁶²⁰ (with low yields of stable Tc complexes) and diaminedithiol ligands.⁶²¹

Fritzberg introduced the idea of prelabeling a chelate with technetium -99m and then binding the chelate to an antibody.⁶²² The ligand was a dimercaptodiamido propanoate which was radiolabeled; the carboxylic acid of the ligand was activated to the ester, and the prelabeled ligand was then reacted with the amino group of the antibody. Franz, Volkert, Barefield and Holmes used cyclam with a sulfhydryl functional group carrying the prelabeled Tc-99m. This was reacted with activated IgG to yield the labeled antibody.^{623 a} One problem with the latter methods is that the yields of labeled antibody are low. Recently, Abrams et al.^{623 b} developed a method to bind ^{99m}Tc to IgG using a hydrazino nicotinamide derivative of IgG. Reaction of ^{99m}Tc glucoheptonate with the derivatized protein led to a stable ^{99m}Tc label, possibly via a ^{99m}Tc -diazenido linkage. The synthesis of several aryldiazenido technetium complexes was carried out by Nicholson et al.⁶²⁷

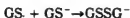
D. After-thoughts on Disulfide Reduction by Sn(II)

In unit activity acid solution (ca. 1M strong acid) the reduction potential of the disulfide-sulfhydryl equilibrium is estimated (not measured) to be about +0.07 volts. In such a solution Sn(II) ($E^\circ \approx 0.15\text{--}0.10\text{v}$) could easily reduce the disulfide to 2 thiols. However, the sulfur system requires an increasingly negative potential with increasing pH for successful reduction. While the simple equilibrium calculation at pH 7, for example, would suggest that Sn(II) is insufficiently reactive by perhaps half a volt, there are several considerations which may change this. In the first place, Scheraga's group^{624 a, b} has shown with cystine-containing hexapeptides that the chemical equilibrium between oxidized and reduced forms can be affected by changing the non-sulfur-bearing peptides. In one case, the equilibrium constant at pH8 was changed from 6.40 to 0.78. . Similar and perhaps larger effects may be found in actual proteins. In the second place, the presence of supporting ligands like histidine and favorable structures could make the reduction by Sn(II) more facile. In the same vein, the very environment of the protein, in the sense that the dielectric constant may be lower, would render reduction easier. Thus, Sawyer showed that a disulfide would be reduced electrolytically at very negative potential in acetonitrile, but could not be reduced in water.⁶²⁵ Lastly, the effect of favorable kinetics may supersede an unfavorable equilibrium constant. Thus, aminopyrine is easily oxidized by H_2O_2 to form a stable radical cation. However, the radical disappeared in seconds in the presence of glutathione.

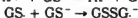
The equilibrium of the following reaction:



is far to the left. However, the reaction



removes GS^- very quickly - and so one kinetically drives a thermodynamically unfavorable reaction to completion.



E. Recent Advances

Two important advances led to the rapid proliferation of ^{99m}Tc in Nuclear Medicine: the development of a generator that could be eluted with saline ^(626a, 626b) and the development of a single vial containing both stannous ion as the reducing agent and the chelating agent. ⁽⁶²⁷⁾ These so called 'instant kits' produce a high yield radiopharmaceutical in one step upon the addition of pertechnetate. Many of these compounds were chosen to trace the function of the excretory organs. However, these functional studies were often confused with efforts to obtain anatomical detail, and in cases in which anatomical changes occurred at the same rate as functional changes, the higher resolution techniques of computed tomography (CT) and, more recently, nuclear magnetic resonance (NMR) imaging have become the diagnostic modality of choice.

There are cases, however, in which function changes more quickly than anatomy, e.g., in bone metastases. Here, nuclear medicine remains an important adjunct to diagnosis. Nevertheless, it is clear that nuclear medicine must concentrate on the measurement of small vessel perfusion and biochemical reactions because that is the source of its uniqueness. Iodinated contrast agents have not progressed beyond polar compounds that distribute in the extracellular space and then are filtered by the glomeruli. Contrast agents for NMR imaging are presently at the same stage of development with, e.g., Gd-DTPA. ⁽⁶²⁸⁾ Agents comparable to the nuclear medicine agents used for hepatobiliary studies, namely Gd and Fe chelates with increased lipophilicity, are now being tested. ⁽⁶²⁹⁾ Because of the lesser requirements for the amount of contrast agent per kilogram of body weight for NMR imaging compared to CT, it may be possible to study small vessel perfusion or biochemical reactions using proton NMR with paramagnetic contrast agents.

Certainly, the present agents, such as ^{99m}Tc sulfur colloid, ^{99m}Tc macroaggregated albumin, ^{99m}Tc DADS [N, N' -bis(mercaptoacetamido)-ethylenediamine], and the ^{99m}Tc bone agents distribute proportional to flow and are most useful to detect flow differences. Two major target tissues, the myocardial muscle and the cerebrum with a normal blood-brain barrier, are now being studied with ^{99m}Tc labeled compounds. In the heart, ^{201}Tl as the thallous cation is used. However, ^{99m}Tc cations, such as hexakis (2-methoxy-2-methylpropyl isonitrile [also known as Cardiolite and RP-30] ⁽⁶³¹⁾ and neutral ^{99m}Tc complexes such as [bis(1,2-cyclohexanedionedioximate(1-)-O)-1,2-cyclohexane-dione-dioximate(2-cyclohexane-dione-dioximate(2)-O)methylborate(2-)-N,N',N'',N''',N''',N''']-chlorotechnetium (one of a class of boron adducts of technetium dioximes [BATOs] also known as Cardiotec, SQ 30.217 or CDO-MeB) ^(632, 634) are being tested to determine their suitability as myocardial perfusion agents. RP-30 is taken up by the myocardium and retained with a half-life of greater than 12 hours, ⁽⁶³¹⁾ whereas ^{99m}Tc -labeled CDO-MeB is taken up rapidly and released rapidly. ⁽⁶³³⁻⁶³⁷⁾ This latter compound is more characteristic of xenon than of thallium and can be used to obtain rapid repeat studies. Both are now approved and are expected to expand nuclear medicine diagnostic studies significantly.

^{133}Xe is approved by the US FDA for the measurement of cerebral perfusion. Recently, ^{123}I labeled *N*-isopropylamphetamine (Spectamine) became the second commercially available agent that crosses the intact blood-brain barrier.^{63b} The distribution immediately after injection is flow related, but the immediate uptake and later distribution are dependent on amine uptake processes. Recently, a number of neutral $^{99\text{m}}\text{Tc}$ labeled compounds were proposed for measuring cerebral blood flow in disease states in which the blood-brain barrier is intact. The series of propyleneamineoximes are interesting cerebral perfusion agents.^{63b} Whereas $^{99\text{m}}\text{Tc}$ PNAO (propyleneamine oxime) is taken up efficiently and released from the cerebrum rapidly, a derivative, $^{99\text{m}}\text{Tc}$, *d,l* hexamethylpropyleneamine oxime (HMPAO) is taken up and retained.^{64b} Because of the available rotating SPECT instrumentation, the latter compound is being studied in the clinic. Another derivative of the BATO series, [bis[2,3-butanedione dioximate(1)-O]-2-methyl, 1-propylborato(2-)-*N*, *N'*, *N''*, *N'''*, *N''''*]-chlorotechnetium SQ 32,097 (also known as Neurovue, SQ 32,097 or DMG-2MP)^{64c} is taken up efficiently by the brain, but the release is slow enough to facilitate SPECT imaging. Finally, there is an ester derivative of the diamino, disulfide chelation system (*N*, *N'*-1,2 ethylenediyl-bis-*L*-cysteine diethylester, Neurolite and *Tc*-ECD)^{64d} that is taken up in the human brain. This compound depends on the slow hydrolysis of the ester groups in the blood and the rapid hydrolysis of ester groups in the brain to give high cerebral uptake and retention of the more hydrophilic metabolite. It appears that a series of first generation $^{99\text{m}}\text{Tc}$ compounds have been developed to measure perfusion in the brain; these hold great promise for establishing the usefulness of nuclear medicine studies of cerebral perfusion in diseases that do not disrupt the blood-brain barrier.

The measurement of biochemical reactions using $^{99\text{m}}\text{Tc}$ has proven difficult. The number of attempts to radiolabel biochemicals that did not result in a true tracer is legendary. Attempts to label fatty acids alone comprise at least 15 $^{99\text{m}}\text{Tc}$ bifunctional chelates, none of which are recognized as fatty acids by the body.^{64e} The expedient path here is to use ^{123}I . Although this radionuclide has ideal imaging properties, it is not available via a generator system. This lack of availability puts it well behind $^{99\text{m}}\text{Tc}$ and, in fact, behind the positron-emitting radionuclides ^{11}C , ^{13}N , ^{15}O , and ^{18}F because these are at least available from an on-site, although expensive, generator, i.e., a small biomedical cyclotron. Nevertheless, ^{123}I seems to be an efficient radionuclide for labeling biochemicals. Many iodinated derivatives of biochemicals have been prepared.^{64f} Many radioiodinated estrogens and progestins have been tested and shown to retain their biochemical reactivity.^{64g,64h} None of these have been tested for disease sensitivity and selectivity, but anecdotal information of their usefulness has been published. To date, $^{99\text{m}}\text{Tc}$ has not been used to label biochemicals (except for $^{99\text{m}}\text{Tc}$ neogalactalbumin) but has been used extensively as a label for perfusion studies.

XIV.

Structure and Stereochemistry in Technetium Coordination Complexes

(Chapter contributed by D.P. Nowotnik and S.S. Jurisson)

A. Introduction

The importance of chemical structure to pharmacological action of drugs has been known for decades. The annals of drug discovery abound with reports showing the influence of physico-chemical parameters, such as charge, lipophilicity, and size, as well as stereochemical considerations (simply, the arrangement of constituent atoms relative to one another) to pharmacological activity. Development of these structure-activity relationships (SARs) have become of paramount importance to the discovery of new or improved pharmaceutical compounds.

Compared to the drug discovery area, the use of technetium in nuclear medicine is a young field. However, there are already many examples where some relationship between complex structure and biodistribution (so-called structure-distribution relationships, or SDRs) have been determined (647-649). As knowledge of the structure of technetium complexes is central to the development of reliable SDRs, ^{99}Tc chemistry has played, and continues to play, a vital role in the discovery of new technetium radiopharmaceuticals. Despite being a weak β -emitter, ^{99}Tc can be studied and characterized by most conventional spectroscopic techniques. For definitive structural information, x-ray crystal structure analysis remains the single most important technique for the characterization of technetium complexes. The Cambridge Structure Library (a database containing a large proportion of all reported structures obtained by x-ray crystal diffraction analysis) contains 148 structures of technetium complexes (June, 1990). In addition to this source, several reviews of ^{99}Tc chemistry have documented the expansion of data associated with technetium chemistry (10a, 10b, 295, 650-658). These reviews, and, in particular, the earlier chapters of this volume, provide a comprehensive appraisal of technetium chemistry, and the structures of technetium complexes.

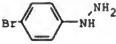
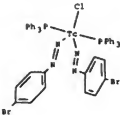
In the following section, several examples of technetium complexes are shown to demonstrate the diversity of its chemistry. Where possible, the structures of known technetium radiopharmaceuticals (i.e. compounds commercially-available or in development) are shown, together with many other complexes described in previous chapters.

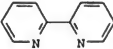
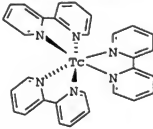
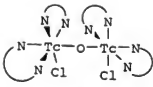
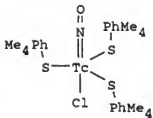
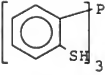
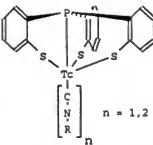
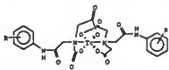
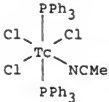
B. The Structure of Technetium Complexes

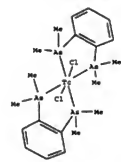
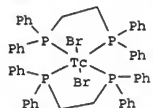
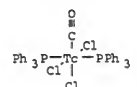
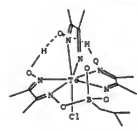
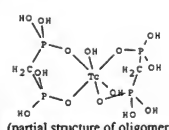
The following table summarizes the chemistry of technetium in terms of particular combinations of metal oxidation state and coordination number:

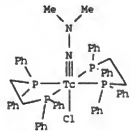
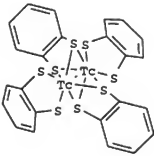
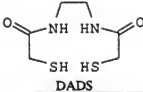
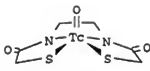
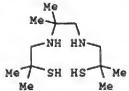
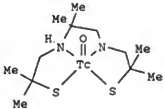
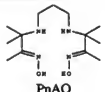
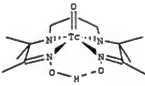
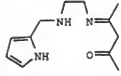
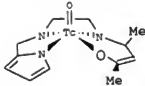
Oxidation state (electronic configuration)	Coordination number					
	4	5	6	7	8	9
-1 (d^8)		X				
0 (d^7)			X			
1 (d^6)			X			
2 (d^5)			X			
3 (d^4)		X	X	X		
4 (d^3)	X		X	X		
5 (d^2)		X	X		X	
6 (d^1)	X	X	X			
7 (d^0)	X	X	X			X

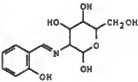
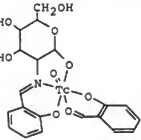
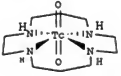
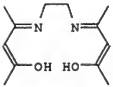
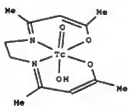
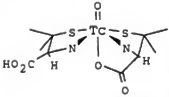
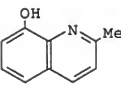
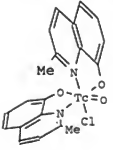
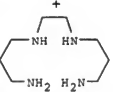
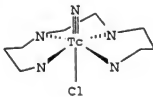
The following table contains representative examples of several of these oxidation state/coordination combinations. Details of the chemistry yielding the complexes shown are (generally) described in detail in preceding chapters, so only the ligand or starting materials which provide the complex are shown in this table. The table also includes information on the charge of the complex; these data are either obtained from the original source or calculated by the authors.

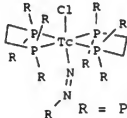
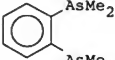
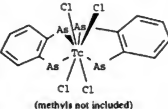
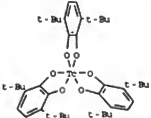
Oxidation state	Coord. number	Geometry	Ligand or starting material(s)	Complex charge	Complex	Reference
-1	5	trigonal bipyramid	$\text{TcCl}_4(\text{PPh}_3)_2 +$ 	0		659
1	6	sandwich	Benzene	+1		542
1	6	octahedral	RNC (alkylisocyanide) for example, $\text{R} = \text{t-Bu}; \quad \text{TB1}$ $\text{R} = \text{MeO}-\text{C}(\text{Me})_2-\text{CH}_2-; \text{MIBI}$	+1		660

2	6	distorted octahedral	$\text{TcCl}_3(\text{CH}_3\text{CN})(\text{PPh}_3)_2$ 	+2		661
2	6	distorted octahedral	$\text{TcCl}_2(\text{bpy})_2$ in water. $\text{bpy} = $ 	0		662
3	5	Trigonal bipyram	$(\text{Bu}_4\text{N})(\text{Tc}(\text{NO})\text{Cl}_4) +$ 2,3,5,6-tetramethylphenylthiol	0		663
3	5 6	Trigonal bipyramid	 $+ \text{R}-\text{N}\equiv\text{C}$	0		664
3	6	distorted octahedral	 HIDA	-1		665
3	6	octahedral	$\text{TcCl}_4(\text{PPh}_3)_2$	0		661, 666

3	6	octahedral	 diars	+1		494
3	6	octahedral	$\text{Ph}_2\text{PCH}_2\text{CH}_2\text{PPh}_2$ (DPPE)	+1		507
3	6	octahedral	$\text{TcCl}_3(\text{PPh}_3)_2(\text{CH}_3\text{CN})$ + CO	0		666
3	7	pentagonal bipyramid	$\text{Tc}(\text{S}_2\text{CNEt}_2)_2\text{N} + \text{SOCl}_2$ or S_2Cl_2	-1		667
3	7	capped trigonal prism	Template reaction from a dioxime, a boronic acid, a halide ion, and TcO_4^-. (BATO)	0		668, 669
4	6	distorted octahedron	 MDP $(\text{NH}_4)_2\text{TcBr}_6$	<0	 (partial structure of oligomer)	670

4	6	octahedron	$\text{TcOCl}_4^- + \text{Me}_2\text{NHNH}_2 + \text{DPPE}$	+3		671
4	7	trigonal prismatic		0		672
5	5	square pyramidal	 DADS	-1		282, 673
5	5	distorted square pyramidal	 DADT	0		674
5	5	square pyramidal	 PnAO	0		319, 319a, 675
5	5	square pyramidal	 MRP20	0		676

5	6	distorted octahedral		-1		677
5	6	distorted octahedral	 cyclam	+1		311
5	6	distorted octahedral	 (acac)₂enH₂	+1		326
5	6	distorted octahedral	 Penicillamine	0		266
5	6	distorted octahedral	TcOCl₄⁻ 	0		322
5	6	octahedral	TcNCl₂(PPh₃)₂ 	+1		678

5	6	distorted octahedron	$\text{TcOCl}_4^- + \text{dppe}$ + phenylhydrazine		679
5	8	 diARs	+1	 (methyls not included)	341a
6	5	$\text{NH}_4\text{TcO}_4 + \text{cHCl} +$ NaN_3	-2		222
6	6	 3,5-di-t-butylcatechol	0		680

C. Stereochemistry in Technetium Complexes

The influence of stereochemistry on the pharmacological action of drugs is well known⁽⁶⁸¹⁾. In nuclear medicine, there were no examples that stereochemistry had any influence on the distribution properties of technetium chelates prior to the 1980s. But recent studies with the complexes of several new ligands, such as $\text{CO}_2\text{-DADS}$ ^(665, 673, 682, 683), NEP-DADT ^(238c, 684), HM-PAO ⁽⁶⁸⁵⁾, and ECD ⁽⁶⁸⁶⁾, have demonstrated that marked differences in biodistribution can exist between the different stereochemical forms of a technetium complex⁽⁶⁸⁷⁾.

Several factors can influence the stereochemistry of metal complexes; ligand stereochemistry, the number, type, and arrangement of donor atoms, chelate ring size and conformation, the coordination geometry of the metal, and, of course, the number of possible ways a ligand can wrap around the metal. With all these eventualities, it is not always possible to develop guidelines on metal stereochemistry. The only reasonable form of analysis involves the examination of individual complexes, as shown in a review of a relatively small set of transition metal complexes⁽⁶⁸⁸⁾.

An understanding of the stereochemistry of metal complexes requires some knowledge of the nomenclature and terms used in naming stereoisomers. As a result, the following two sections have been included to provide an introduction to the principles and nomenclature. The first of these two sections is loosely termed 'organic stereochemistry'. It is primarily intended to examine stereochemistry in ligands, which will impact upon

the stereochemistry of metal complexes. The section on 'inorganic stereochemistry' deals with stereochemical issues specific to metal chelates.

1. Organic Stereochemistry Nomenclature

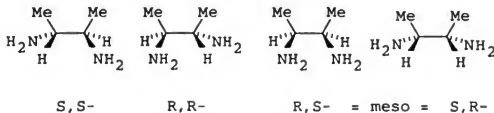
There are two types of isomerism (isomers = compounds which share the same molecular formula); constitutional isomers are compounds which differ because their atoms are connected in a different order; stereoisomers have their constituent atoms connected in exactly the same way, but differ in the arrangement of these atoms in three-dimensional space (689).

The term 'constitution isomers' can also be applied (with subtly different meaning) to metal chelates (see section 3). When applied solely to the ligand, constitutional isomers are not stereoisomers; they are distinctly different compounds, which have different physical and chemical properties. For the purpose of this review, ligand constitution isomers will not be considered apart from a brief examination of a sub-class of constitutional isomer; the positional isomers. For ligands, this term applies to isomeric organic compounds which have a common donor set (i.e. the donor atoms are in the same sequence, with the same carbon backbone), but have a different arrangement of substituents.

If two stereoisomers are 'mirror-images' of each other, they are termed enantiomers; two stereoisomers which are not 'mirror-images' are termed diastereoisomers. The simplest example of an enantiomer is an organic compound which has one tetrahedral carbon atom containing four different substituents, for example 2-chlorobutane. An important physical property of enantiomers is that, in solution, they will cause the plane of polarized light (passed through that solution) to be rotated. The degree of rotation is equal and opposite in a pair of enantiomers. A solution containing a mixture of equal quantities of the two enantiomers (racemic mixture) has no effect on the plane of a beam of polarized light. There is no relationship between the absolute configuration of a molecule, and the direction of light rotation. However, the direction of rotation can be used to characterize a stereoisomer of unknown absolute stereochemistry. Enantiomers may be termed *d*- (dextrorotatory) or (+) if the plane of polarized light is rotated clockwise, or *l*- (levorotatory) or (-) if rotation is anticlockwise. A racemic mixture is denoted *dl*- or ($\pm$).

There are two conventions in use for naming absolute configuration. The traditional method uses *D*- or *L*- (sometimes confused with *d*- and *l*- in radiopharmaceutical literature!). However, as a result of confusion in the rules for using this system, the Cahn-Ingold-Prelog convention (*R*- and *S*-) system is now more usual. Substituents attached to an asymmetric atom are ordered in a priority sequence. Priority is given to substituents of highest atomic number. The molecule is then viewed from the side opposite the atom of lowest priority; if the substituents of increasing priority appear in clockwise sequence, the configuration is denoted '*R*'; an anticlockwise sequence of priority is denoted by '*S*'. One difficulty with this system is that a small change in the molecule some distance away from the chiral center can result in a change of the *R* or *S* designation.

A molecule with *n* chiral centers has, potentially, 2^n stereochemical forms. The number of isomers will be less than this in molecules with the potential for a symmetrical arrangement of atoms. An example: 2,3-butanediamine has two chiral centers, but only 3 stereoisomers. The *R,R*- and *S,S*- forms are enantiomers, but the *R,S*- and *S,R*- are equivalent. The *R,S*-form is optically inactive, due to internal compensation, and is often termed the *meso*-form.



2. Inorganic Stereochemistry Nomenclature

Stereoisomers (or optical isomers), as defined above, are chemically the same compound, differing only in their orientation in three dimensional space. For an enantiomer not to be superimposable on its mirror image, it must have either no symmetry or possess only a proper rotation axis (belong to the symmetry groups C_n or D_n). Stereochemistry that is determined solely by the metal complex is coordination number dependent.

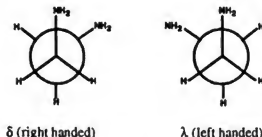
Much of the nomenclature has been coined for six-coordinate octahedral complexes containing two or more bidentate chelates (eg, ethylenediamine (en)). As is true for organic compounds, the simplest method for identifying an enantiomer is to define the direction of rotation of plane polarized light, namely + or d, - or l. This method does not, however, define the absolute configuration of the complex. For example, the two enantiomers of $[\text{Co(en)}_3]^{3+}$ and $[\text{Rh(en)}_3]^{3+}$ that rotate sodium D light in the same direction are known to have the opposite absolute configuration; they are enantiomers of each other, except for the metal.

The more accepted method of assigning the absolute configuration is to view the tris chelate complex down the threefold rotation axis. If the helix that is observed is right-handed, the isomer is Δ , and its mirror image is the Λ isomer.



Ordinary diffraction analyses provides no information on the absolute configuration about the metal since both enantiomers give the same diffraction pattern.

In addition to the configuration about the metal center, the conformation of the chelate rings can impart asymmetry to the molecule. If we consider the gauche form of ethylenediamine, the right handed conformation is termed δ and the left handed conformation is λ .



Theoretically, this leads to eight isomers for an octahedral tris chelate complex: $\Delta\delta\delta\delta$, $\Delta\delta\delta\lambda$, $\Delta\delta\lambda\lambda$, $\Delta\lambda\lambda\lambda$, $\Lambda\delta\delta\delta$, $\Lambda\delta\delta\lambda$, $\Lambda\delta\lambda\lambda$ and $\Lambda\lambda\lambda\lambda$. Because of steric interactions we observe only the $\lambda\lambda\lambda$ and $\delta\delta\delta$ conformations, resulting when including the Δ and Λ configurations. In addition, any substituents that are larger than hydrogen will cause the chelate ring to adopt the orientation about the metal in which the larger substituents are in the equatorial position. To further define the absolute configuration of the metal complex, the orientation of the three chelates about the metal in the form of a left handed helix is termed *lel* because the C-C bonds of the

chelate are parallel to the threefold axis of the metal complex. If the arrangement of ligands forms a right handed helix about the metal, it is termed *ob* because the C-C bonds are oblique to the three-fold axis.

Since most technetium complexes (and especially those with radiopharmaceutical applications) are not octahedral tris chelates or octahedral bis chelates with two monodentate ligands in a *cis* arrangement, very little if any attention has been paid to absolute configuration in these complexes. For example, the technetium(I) complex $[Tc(dmpe)_3]^+$ should have two isomers: $\Delta\lambda\lambda$ and $\Lambda\delta\delta$.

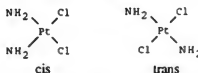
More applicable to technetium chemistry and radiopharmaceuticals is the stereochemistry associated with square planar complexes, since this nomenclature can be extended to the five-coordinate, square pyramidal $Tc(V)O$ complexes. For these complexes, the configuration about the metal (Δ or Λ) is no longer an issue. The possible ligand configurations for a square planar bis chelate complex are then $\lambda\lambda$, $\delta\delta$, $\lambda\delta$ and $\delta\lambda$. There are in fact only three isomers because the $\lambda\delta$ and $\delta\lambda$ configurations are identical. These would not be identical for the five-coordinate square pyramidal $Tc(V)O$ complexes. The $\lambda\lambda$ and $\delta\delta$ complexes are enantiomers of each other, while the $\lambda\delta$ configuration is termed *meso*. In general, the steric interactions of the ligands in a *meso* configuration slightly destabilize this arrangement relative to the $\lambda\lambda/\delta\delta$ (*d,l*) orientation.

The oxo group in the axial position of five-coordinate $Tc(V)$ complexes imparts an additional type of conformation to the chelate ring(s) when the chelates contain different substituents on any one of the backbone atoms. These substituents can be oriented *syn* (same side) or *anti* (opposite side) to the Tc-oxo bond. This nomenclature is already in use with the $Tc(V)$ BAT and DADT complexes.

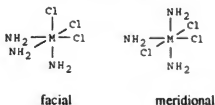
3. Constitutional Isomers

Constitutional isomers are comprised of molecules that are chemically and physically different; they are made up of the same atoms, simply bonded in a different manner to the metal. Geometric and linkage isomers are the two major types of constitutional isomers.

The most common type of geometric isomerism is that of the *cis/trans* type often observed in square planar (4-coordinate) and octahedral (6-coordinate) complexes. A metal complex is said to have a *trans* configuration of the ligands if two like groups are situated opposite each other in a plane including them and the metal, and a *cis* arrangement if the two ligands are next to each other.



Another type of geometric isomerism that is observed in octahedral complexes having three identical groups coordinated to the metal is meridional/facial isomerism. The meridional (*mer*-) isomer is observed when the three identical groups bound to the metal lie in the same plane. The facial (*fac*-) isomer has the three identical groups occupying the face of the threefold axis of the metal complex.

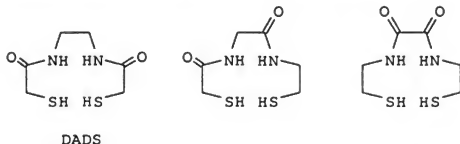


Linkage isomers are possible when ligands are capable of binding to the metal in more than one way and with different donor atoms. Examples include thiocyanate/isothiocyanate ($M\text{-SCN}/M\text{-NCS}$) and nitro/nitrito ($M\text{-NO}_2/M\text{-ONO}$). Generally, one of the linkage isomers will be thermodynamically favored, although under specific conditions one, the other or both might exist.

4. Positional Isomers

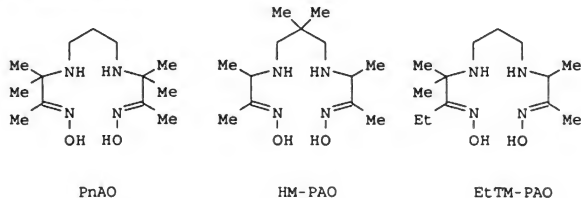
As defined earlier, positional isomers are, in the strict sense, not stereoisomers. However, complexes from such isomers do share some of the features of stereoisomers. Complexes from a set of positional isomers can have the same molecular weight, size, lipophilicity, charge, and general shape. Under these circumstances, like stereoisomeric complexes, any differences in the biodistribution of these complexes result from the different spacial orientation of substituents. The following two examples demonstrate the concept of positional isomers in technetium chemistry:

Initial studies of the technetium chemistry of the diamidedithiol (DADS) ligand, shown below, demonstrated that the $Tc(V)O$ complex was formed in high yield (282, 690); in addition, that complex was shown to have promising properties as a renal function imaging agent (691). Analogues of the original DADS ligand were prepared, in which the position of the carbonyl groups on the carbon backbone were altered. These ligands, like DADS, provided monoanionic $Tc(V)O$ complexes (673).



In these examples, all the nitrogen atoms are amides, and so, in their technetium complexes, these donor atoms will have planar trigonal geometry. As a result, there is not expected to be any conformational differences in the chelate ring formed by the two nitrogen atoms in these complexes.

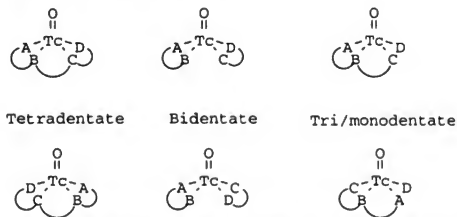
Another example of a series of positional isomers can be found in the propylene amine oxime (PnAO) ligands, and their complexes. Three ligands (639, 692, 693) from the large number of PnAO derivatives prepared (685) are shown below:



These amine oxime ligands are positional isomers. Unlike the series of DADS ligands, described above, the core of the Tc(V)O complexes formed from these ligands (i.e. the complexes without alkyl substituents) are virtually superimposable (319), so these complexes differ only in the position of their alkyl substituents. The position of these substituents has a marked influence on the biodistribution properties of these complexes. All three complexes cross the blood-brain barrier in rats (639, 692, 693). TcOPnAO is not retained, and demonstrates rapid efflux from the brain (639), whereas the complexes of other two PnAO derivatives show some cerebral retention (641, 649). TcO-HM-PAO demonstrates cerebral uptake and retention in rats, man, and baboons (641, 693, 694), whereas species differences are observed in the case of TcO-EiTM-PAO; the latter complex demonstrates brain uptake and retention in rats (693), and baboons (694), but not in man (695). Both HM-PAO and EiTM-PAO possess chiral centers, which give rise to stereoisomers, as described later.

5. Stereochemistry in Tc(V)O Complexes

The majority of examples of technetium complexes where stereochemistry is known to influence the biodistribution appeared in studies over the past decade on Tc(V)O complexes. This bias reflects the amount of effort expended on this core towards the development of new radiopharmaceuticals, primarily due to the accessibility of Tc(V) complexes from pertechnetate. Tc(V)O complexes may be formed from mono-, di-, tri-, and tetradentate ligands. The more usual examples are:

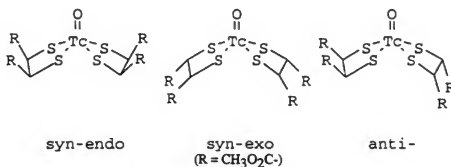


In all 3 cases, stereoisomeric complexes are possible. With tetradentate and tri/monodentate complexes, depending upon the symmetry of the ligand, at least the two complexes shown are possible, provided that inversion of the TcO core does not take place. In TcO complexes with bidentate ligands, donor A can be *cis*- or *trans*- to donor D, giving 2 possible stereoisomers. More stereochemical forms are possible if the ligands possess chiral centers and/or more than one conformational form is possible. Few examples are known of tri/monodentate Tc(V)O complexes (325, 696), so our review will concentrate on bis-complexes of bidentate ligands and tetradentate ligands.

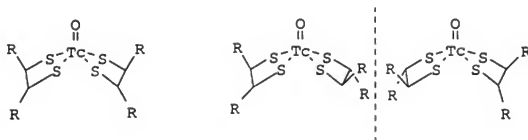
Several Tc(V)O complexes of thiol containing bidentate ligands have been prepared, for example, ethane-1,2-dithiol (278), mercaptoacetic acid (26), 2-mercaptoethanol (280), and 2-mercaptoethylamine (697). In the case of the S,O ligands, the *cis*-isomers were isolated, although nmr evidence also indicated the presence of the *trans*- forms of these complexes.

The introduction of substituents onto the carbon backbone (one substituent per carbon atom) of bidentate ligands will create chiral centers in these ligands, and provide a number of possibilities for stereoisomeric complexes. The Tc(V)O complexes of dimercaptosuccinic acid (DMSA), and its esters, have provided a number of stereoisomeric complexes. *meso*-DMSA has two chiral centers, but is not optically active due to internal

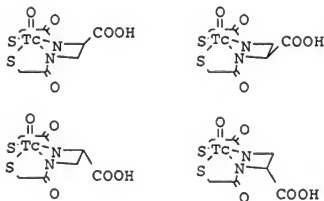
compensation. However, there are a number of stereochemical possibilities for the Tc(V)O-complex of meso-DMSA (methyl ester) (279);



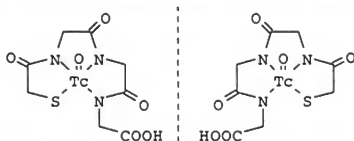
The syn-endo complex was the major isomer produced, and an X-ray crystal structure was obtained of this complex (279). Subsequently, a ¹H nmr study demonstrated the presence of the other two isomers as well as the syn-endo-form when the ⁹⁹Tc complex is prepared in a ligand exchange process with Tc-gluconate (698). In methanol containing an amine, the ligand in the syn-endo-complex racemises from the meso- to the d,l-form; two stereoisomeric forms of d,l-DMSO were identified by ¹H nmr, although one of these two forms will be a mixture of two enantiomers (698).



The first example of stereoisomerism in Tc(V)O complexes from tetradentate ligands came as a result of studies to improve upon the renal clearance characteristics of Tc-DADS. Fritzberg et al produced a DADS derivative containing a carboxyl substituent; the ligand, termed CO₂DADS (699) provided two ^{99m}Tc-complexes, which could be separated by HPLC, and, when separated, demonstrated different renal clearance properties. FAB Mass spectrometry showed that the two complexes were identical, and they were assigned as cis- and trans-epimers (665), confirmed subsequently by a full structural study (700, 701). Originally, CO₂DADS was produced from a racemic mixture of 2,3-diaminopropionic acid; when this ligand was prepared from L- and D-enantiomers of this starting material, Verbruggen et al (683) demonstrated that four stereoisomers could be formed, resulting from the formation of syn- or anti- orientation of the carboxyl relative to the oxygen of the TcO core, and from either the D- or L- form of the ligand. Differences in the biodistribution properties of these stereoisomeric complexes were noted (683).



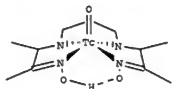
Other C-substituted DADS derivatives have been synthesized, but all suffered from problems associated with the formation of mixtures of stereoisomeric complexes^(682, 702-704). Recognising that the potential to form mixtures of stereoisomers was an undesirable feature in the development of new radiopharmaceuticals for renal function studies, Fritzberg et al developed the ligand MAG₃⁽⁷⁰⁵⁻⁷⁰⁶⁾, a ligand which contained no chiral center. That radiopharmaceutical, now developed as a commercial product by Mallinckrodt, is in routine use as a technetium replacement for Hippuran. However, as the donor set in MAG₃ is not symmetrical, this ligand does form a mixture of enantiomeric Tc(V)O complexes. The individual enantiomers of ^{99m}Tc-MAG₃ have been isolated⁽⁷⁰⁷⁾. Racemization of the isomers (i.e. inversion of the Tc=O core) does take place under relatively mild conditions, and, so, it is not surprising that only minor differences are seen in the renal clearance properties when each enantiomer is administered separately to baboons or a human volunteer⁽⁷⁰⁷⁾.



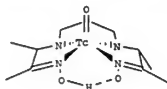
Additional stereoisomers may be formed by making derivatives of MAG₃ with single substituents on the carbon backbone; a number of these ligands have been made from stereochemically-pure starting materials, and their ^{99m}Tc-complexes resolved into syn- and anti- derivatives^(707, 708). Again, biodistribution studies of the isolated, single stereoisomer complexes demonstrate the importance of stereochemistry on distribution^(707, 708).

One area of research that has also been fruitful in demonstrating a biodistribution dependence on stereochemistry has been technetium brain perfusion tracers. The major area of study has concentrated on the development of tetradentate ligands for the formation of neutral, lipophilic complexes capable of crossing the blood-brain barrier. Two ligands have dominated this area; propylene amine oxime (PnAO) and diamine dithiols (DADT). As described in the last section, the ligand HM-PAO provided a technetium complex with the desirable feature of high brain uptake, with good retention of activity for SPECT⁽⁷⁰⁹⁾. As HM-PAO has two chiral centers, it can form up to four possible stereoisomers. Two of these possible stereoisomers are identical (the meso form), while the other two are enantiomers, differentiated only by their ability to rotate polarized light, d- and l-HM-PAO⁽⁷¹⁰⁾.

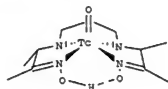
The four nitrogen atoms in the technetium complexes of propylene amine oximes are sp^2 (all bonds lie in one plane), and so there is no opportunity for this ligand to form conformational isomers. The stereochemistry of these ligands is associated with achirality of the ligand. Hence, there is a single stereoisomeric form of Tc-PnAO, but, as mentioned earlier, there are three isomers of HM-PAO, and its analogue, TM-PAO:



Tc-meso-HM-PAO



Tc-d-HM-PAO



Tc-l-HM-PAO

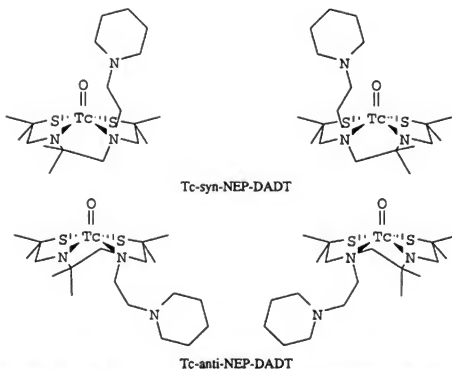
(As the absolute stereochemistry of d- and l-enantiomers are unknown, the assignments of d- and l- shown here are arbitrary)

The meso-form of these ligands are achiral, but are capable of forming two stereoisomeric Tc=O complexes, with the methyl groups being either syn- or anti- to the oxygen atom of the Tc=O core. However, the meso ligands appear to form only one complex, with the methyl groups in the syn-orientation⁽⁵⁰⁹⁾. The anti-form may be thermodynamically disfavoured due to crowding of the methyl groups on the side of the molecule anti- to the Tc=O core. In the solid state, two conformational isomers of ^{99}Tc -meso-HM-PAO were noted; the six-membered ring made up of Tc, two nitrogen atoms and the propylene bridge was in the chair-form in one case, and the boat form in the other⁽⁵⁰⁹⁾. Presumably, there is rapid interconversion between these forms in solution.

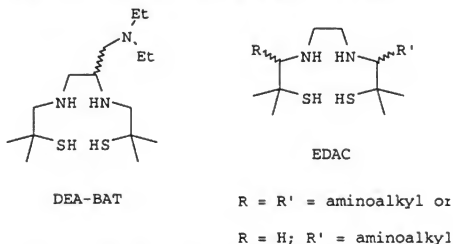
The d- and l- isomers of HM-PAO each form only one stereoisomeric complex; each has one of the methyls α -to the amines syn- and the other anti- to the Tc=O core⁽⁵⁰⁹⁾. The d- and l- complexes are enantiomers. In its commercially available form, HM-PAO is sold as a racemic mixture of the d- and l- enantiomers, despite the fact that there is some evidence that *in vivo* properties of the two enantiomeric complexes are not the same⁽⁶⁹²⁾.

The other tetradentate ligand for the Tc(V)O core to be extensively studied is DADT. This ligand contains two amines and two thiol ligands. It forms a neutral complex (neutralising the +3 charge of the core) by deprotonation of the two thiols, and one of the amines on complexation⁽⁶⁷⁴⁾. Thus, three of the donor groups in Tc-DADT complexes have sp^3 geometry, while one (the deprotonated nitrogen atom) is sp^2 . Therefore, this ligand theoretically can give rise to more than one stereoisomeric complex due to conformational differences. For tetradentate systems (unlike bidentate ligands), once the conformational geometry of one chelate ring is established, the other two chelate rings usually can only adopt one conformation. This appears to be the case for the DADT system, which provides two conformational technetium complexes.

These conformational differences are seen most clearly in those DADT complexes which have an alkyl substituent on the sp^3 nitrogen atom. For example, the complex NEP-DADT, a DADT derivative with an N-piperidinyethyl substituent, forms two $^{99\text{m}}\text{Tc}$ -complexes (in 8:2 ratio) which can be separated by reverse-phase HPLC^(283b). These complexes do not have identical biodistribution properties^(283b). Preparation and characterization of these complexes at the ^{99}Tc -level demonstrated that the two stereoisomers differed in the orientation of the nitrogen substituent relative to the Tc=O core; the dominant stereoisomer had the syn-configuration^(283c, 711). Examination of these molecules indicates that each may also be a mixture of enantiomeric forms, but no reports have appeared on any attempted resolution of these enantiomers.

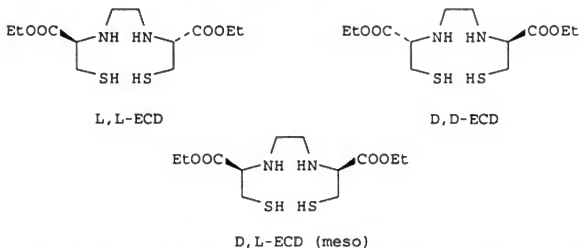


The number of possible Tc-DADT stereoisomers can increase further when substituents are added to the carbon backbone. Single substituents have been placed on the ethylene bridge (between the amine groups, replacing the gem-dimethyls; e.g. DEA-BAT) (712-714), while, in another series of ligands (called EDACs), substituent(s) are added to DADT carbons between the nitrogen and sulfur atoms (715).



There are several factors giving rise to stereoisomerism in these complexes; ring conformation, syn/anti-orientation of the substituent(s) (these factors are now separate, as the substituent is not bound to a donor atom), and the stereochemistry at the asymmetric carbon atom (8 possible stereoisomers). An X-ray crystal structure analysis of an analog of Tc-DEA-BAT has shown two complexes, in which the C-substituents are either syn- or anti- to the Tc=O core, but with the single proton on the nitrogen in the chelate ring in the syn-orientation in both cases (713). No structural characterization of the EDAC complexes have been reported to date, but these, too, could provide several stereoisomeric forms; the situation for the monosubstituted EDACs will be similar to DEA-BAT, while the possible stereoisomers for complexes of disubstituted EDACs will be similar to another DADT ligand, ECD.

ECD (ethyl cysteinate dimer) is a symmetrical ligand with two chiral centers. As the ligand can readily be synthesized from stereochemically pure starting materials (L- or D-cysteine)⁽⁷¹⁶⁾, all stereochemical forms of ECD have been made, and their technetium complexes studied.

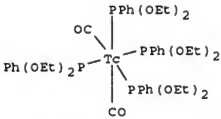
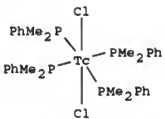
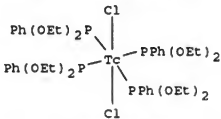
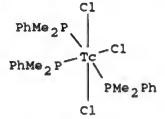
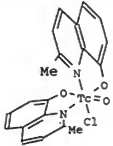
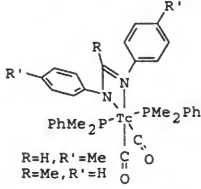
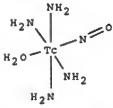
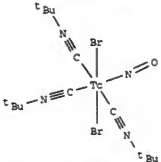


Single stereoisomer technetium complexes are formed with D,D- and L,L-ECD⁽⁷¹⁷⁾. The meso form of ECD could form syn- and anti- complexes, but, like meso-HM-PAO, only one stereoisomer was observed, the syn-isomer⁽⁷¹⁸⁾.

These complexes display remarkable stereoselectivity *in vivo*. All complexes are believed to cross (or have the potential to cross) the intact blood-brain barrier (BBB). *In vivo*, these complexes are hydrolyzed (supposedly by esterases) to the mono acid or diacid⁽⁷¹⁹⁾. When this happens before the molecule has crossed the BBB, the complex is excluded from the brain; if this happens while the complex is in the brain, it is proposed⁽⁷²⁰⁾ that the hydrolyzed complex is retained by the brain; the observed brain retention of the ^{99m}Tc-L,L-ECD in higher species is attributed to intra-cerebral hydrolysis of the tracer⁽⁷²⁰⁾. Using brain homogenates (as the source of the putative esterases), the relative rate of hydrolysis of ECD complexes is L,L- > D,L- > D,D-⁽⁷²⁰⁾. In addition, there are distinct species differences in the behaviour of Tc-ECD complexes, attributed to species differences in esterase concentration and/or 'activity'⁽⁷²⁰⁾. Recently, it was found that the Tc-complexes of the diacid form of ECD display interesting renal clearance properties⁽⁷²¹⁾. Again, the clearance rate is influenced by stereochemistry; the most promising is the L,L-isomer complex, which appears to clear faster than does Tc-MAG₃.

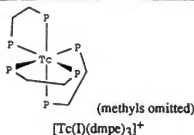
6. Stereochemistry in Octahedral Technetium Complexes

Several examples have been reported where the possibility of geometric isomerism does exist. Below are shown some examples where either (or both) cis/trans- or mer/fac- isomers have been reported in octahedral complexes. In several examples, involving saturated chelate rings, λ/δ conformational isomers might also be formed. Detailed discussion of the factors giving rise to cis/trans or mer/fac geometry appear in a number of the papers cited. As a general rule, however, it appears that trans-geometry tends to dominate technetium chelate chemistry.

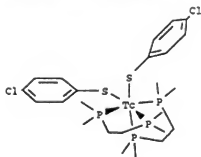
 <i>cis</i>-[Tc(II)(CO)₂(PPh(OEt)₂)₄]⁺ Biagini Cingi et al (514)	 <i>trans</i>-Tc(IV)Cl₂(PMe₂Ph)₄ Mazzi et al (468)
 <i>trans</i>-Tc(II)Cl₂(PPh(OEt)₂)₄ Mazzi et al (722)	 <i>mer</i>-Tc(III)Cl₃(PMe₂Ph)₃ Bandoli et al (500)
These two complexes were prepared under similar conditions. Bandoli et al (500) discuss the factors which influence coordination geometry, and attribute the differences, primarily, to the electronic and steric distinctions between phosphine and phosphite (723)	
 <i>cis</i>-Tc(V)OCl(2-methyloxine)₂ Wilcox et al (322)	 <i>trans</i>-Tc(I)(PMe₂Ph)₂(CO)₂(diaz)₂ Marchi et al (552)
 <i>trans</i>-[Tc(II)NO(H₂O)(NH₂)₄]²⁺ Armstrong, Taube (213)	 <i>mer</i>-Tc(I)NOBr₂(TBI)₃ Linder et al (538)



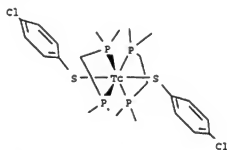
A large number of Tc(II), Tc(III), and Tc(V) diphosphine complexes have been characterized (507, 534, 724, 725). All (except that below) have *trans*-geometry. No stereoisomers have been described, although it is possible that Λ/Δ conformational isomers will exist. Mixtures of stereoisomers will also be formed if the four phosphine substituents are not identical, or if substituents are placed on the ethylene bridge (726)



Few details of the structure of this complex have been published (724, 727). However, it is one of the few examples in technetium chemistry where Λ and Δ forms of a complex could be formed. Therefore, it must be assumed that all biological studies with this complex (727) involved a mixture of these two stereoisomeric forms.

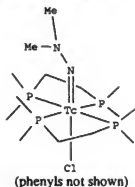


cis-Tc(II)(p-chlorobenzenethiolato)₂(DMPE)₂



trans-Tc(II)(p-chlorobenzenethiolato)₂(DMPE)₂

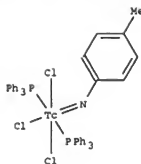
A mixture of *cis*- and *trans*-isomers were obtained on reacting *trans*-Tc(V)O(OH)(DMPE)₂ with p-chlorobenzenethiol under basic conditions (728). When the reagent is an alkylthiol (729), or benzenethiol (730), only the *trans*-isomer of the Tc(III) complex is obtained. Clearly, electronic factors favor Tc(II) over Tc(III) with/without the p-chloro-substituent, while steric factors in the Tc(II) state influences geometry (728)



trans-Tc(MeNN)Cl(DPPE)₂

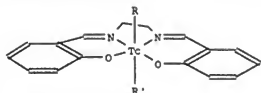
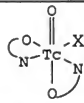
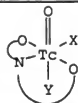
Archer et al (671)

(Note also the possible Δ/Λ conformational isomers in DPPE chelate rings)

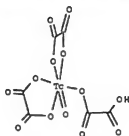
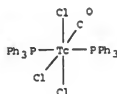
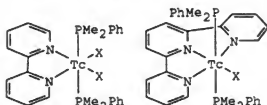
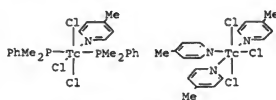


trans-Tc(tolN)Cl₃(PPh₃)₂

Archer et al (671)

Tc(V); R=(O=), R' = Cl, H₂O (326)Tc(III); R = R' = PPh₃ (509)Bi- and tridentate Schiff-base ligands
Mazzi et al (327)

Tetradentate Schiff base ligands (above left) have little opportunity to form complexes other than in the *trans*-orientation, as shown. The conjugated π -system forces the ligand to be planar, so no conformational isomers are possible. By comparison, bidentate Schiff base ligands potentially can provide *mer*- and *fac*- isomeric complexes; tridentate Schiff base ligands will give *mer*-complexes.

*cis*-[Tc(V)O(ox)₂(Hox)]²⁻
Baldas et al (731)*mer*-Tc(III)Cl₃(PPh₃)₂(CO)
Pearlstein et al (666)*trans*-Tc(II/III)(PMe₂Ph)₂(pic/phen)
Wilcox et al (732, 733)*mer*-Tc(III)picoline complexes
Lu et al (734)

BIBLIOGRAPHY

1. Perrier C, Segrè E. Radioactive isotopes of element 43. *Nature* 140, 193-194, 1937.
- 2a. Handbook of Chemistry and Physics, 59th edition. CRC Press Inc. West Palm Beach, Florida, B296, 297, 1978-1979.
- 2b. Table of Isotopes. eds. C. M. Lederer, V.S. Shirley, 7th ed, John Wiley and Sons, New York, 1978.
3. Harper PV, Andros G, Lathrop K. Preliminary observations on the use of six-hour ^{99m}Tc as a tracer in biology and medicine. Argonne Cancer Research Hospital, ACRH-18, 1962, 176-188.
4. Tucker D, Greene MW, Weiss AJ, Murrenhoff A. P. American Nuclear Society Annual Meeting, Los Angeles, CA., June 1958. *Trans. Am. Nucl. Soc.* 1, 1958, 160.
5. Richards, P. A survey of the production at Brookhaven Nat'l Lab. of radioisotopes for medical research. *Trans. 5th Nuclear Congress, 7th Int. Electronic Nuclear Symposium (Rome)*, June, 1960, 255.
- 6a. Richards P, Tucker WD, Srivastava SC. Introduction; Technetium-99m: an historical perspective. *Int. J. Appl. Radiat. Isot.* 33, 1982, 793-799.
- 6b. The Nuclear Medicine Market. Frost and Sullivan, New York, NY, 1988.
7. Dillman LT, Vonder Loge FC. Radionuclide decay schemes and nuclear parameters for use in radiation-dose estimation. *MIRD Pamphlet #10*, 1975, 119.
8. Wagner HN Jr. Present and future applications of radiopharmaceuticals from generator-produced radioisotopes. Panel organized by the International Atomic Energy Agency in Vienna, 11-15 May, 1970, published in 1971, 163-165.
9. Cotton FA, Wilkinson G. *Advanced Inorganic Chemistry*, 3rd ed. Wiley-Interscience, New York, 1988, back page.
- 10a. Jones AG, Davison A. The chemistry of technetium I, II, III and IV. *Int. J. Appl. Radiat. Isot.* 33, 1982, 867-874.
- 10b. Davison A, Jones AG. The chemistry of technetium (V). *Int. J. Appl. Radiat. Isot.* 33, 1982, 875-881.
11. Rucker TL, Mullins WT. Radioanalysis of technetium-99 at the Oak Ridge Gaseous Diffusion Plant. *Radioelem. Anal. Prog. Probl., Proc. Conf. Anal. Chem. Energy Technol.*, 23rd, 1979 (Pub. 1980), 95-100. Edited by Lyons WS. Ann Arbor Sci.: Ann Arbor, Mich.
- 12a. Foti SC, Delucchi E, Akamian V. Determination of picogram amounts of ^{99}Tc by neutron activation analysis. *Anal. Chim. Acta* 60, 1972, 261-268.
- 12b. Foti SC, Delucchi E, Akamian V. Determination of picogram amounts of technetium in environmental samples by neutron activation analysis. *Anal. Chim. Acta* 60, 1972, 269-276.

- 12c. Bate LC. Determination of technetium-99 in mixed fission products by neutron activation analysis. *Radioelem. Anal.: Prog. Probl. Proc. Conf. Anal. Chem. Energy Technol.*, 23rd, 1979 (Publ. 1980), 175-189. Edited by Lyons WS. Ann Arbor Sci.: Ann Arbor, Mich.
13. Hareland WA, Ebersole ER, Ramachandran TP. Determination of technetium by atomic absorption spectrophotometry. *Anal. Chem.* 44, 1972, 520-523
14. Lux F, Ammentorp-Schmidt F, Opavsky W. X-ray fluorescence determination of Tc and Mo in solutions. *Z. Anorg. Allgem. Chem.* 341, 1965, 172-182.
15. Andersen TJ, Walker R L. Determination of picogram amounts of technetium-99 by resin bead mass spectrometric isotope dilution. *Anal. Chem.* 52, 1980, 709-713.
16. Mullen P, Schwochau K, Jorgensen CK. Vacuo ultraviolet spectra of permanganate, pertechnetate, and perhenate. *Chem. Phys. Lett.* 3, 1969, 49-51.
17. Magee RJ, Al-Kayssi M. Determination of rhenium and technetium by infrared spectroscopy. *Anal. Chim. Acta* 27, 1962, 469-473.
18. Crouthamel CE. Thiocyanate spectrophotometric determination of technetium. *Anal. Chem.* 29, 1957, 1756-1760.
19. Tentative method for the colorimetric determination of pertechnetate in aqueous solutions. *Annual Book of ASTM Standards. Part 30* (1973). 5pp. (ASTM-E-417-70-T).
20. Tribalat S. Physicochemical and analytical properties of rhenium. *Ann. Chim.* 4, 1949, 289-351.
21. Schwochau K, Astheimer L, Schenk HJ. Thiocyanato complexes of technetium (IV) and-(V). *J. Inorg. Nucl. Chem.* 35, 1973, 2249-2257.
22. Trop HS, Davison A, Carey GH, et al. Electrochemical studies on halide and pseudo-halide complexes of technetium and rhenium. *J. Inorg. Nucl. Chem.* 41, 1979, 271-272.
23. Trop HS, Davison A, Jones AG, et al. Synthesis and physical properties of hexakis (isothiocyanato) technetate (III) and-(IV) complexes. Structure of the $[\text{Tc}(\text{NCS})_6]^-$ ion. *Inorg. Chem.* 19, 1980, 1105-1110.
24. Davison A., Jones AG, Müller L, et al. Synthesis and characterization of oxopentakis (isothiocyanato) metalate (V) complexes of rhenium and technetium. *Inorg. Chem.* 20, 1981, 1160-3.
25. Miller FJ, Thomason PF. Spectrophotometric determination of technetium (VII) with thioglycolic acid. *Anal. Chem.* 32, 1960, 1429-1430.
26. DePamphilis BV, Jones AG, Davis MA, et al. Preparation and crystal structure of oxotechnetium bis (thiomercaptoacetate) and its relationship to radiopharmaceuticals labelled with technetium-99m. *J. Am. Chem. Soc.* 100, 1978, 5570-5571.
27. Miller HH, Kelley MT, Thomason PF. Polarographic studies of the reduction of pertechnetate ion in aqueous solutions. *Advances in Polarography, Vol.2*, Langmuir IS, ed., Pergamon Press, London, 1960, 716.

28. Astheimer L, Schwochau K, Herr WJ. Polarography of technetium. II. Radiometric determination of self-diffusion coefficients for pertechnetate ions in aqueous solutions. *J. Electroanal. Chem.* **14**, 1967, 161-167.
29. *Gmelin Handbook of Inorganic Chemistry, System Number 69, Tc Technetium, Supplement Volume 2, Metals, Alloys, Compounds, Chemistry in Solution*, Springer-Verlag, Berlin, Heidelberg, New York, 1983, 198-199.
30. Mazzocchin GA, Mazzi U, Portanova R, et al. Quantitative determinations of technetate (VII) and technetium (IV). *J. Inorg. Nucl. Chem.* **36**, 1974, 3783-3788.
- 31a. Friedlander G, Kennedy JW, Miller JM. *Nuclear and Radiochemistry*, Second Edition, John Wiley & Sons, Inc., New York, 1964, 70-73.
- 31b. Boyd RE. Technetium-99m generators - the available options. *Int. J. Appl. Radiat. Isot.* **33**, 1982, 801-809.
32. Baumgaertner F, Fischer EO, Zahn U. Dicyclopentadienylrhodium (II) by conversion of the elements from dicyclopentadienylruthenium(II). *Chem. Ber.* **94**, 1961, 2198.
33. Baumgaertner F, Fischer EO, Zahn U. Aromatic complexes of metals. LVIII. Carrier-free $C_5H_5Tc(CO)_3$ by element conversion from $[C_5H_5Mo(CO)_3]_2$. *Naturwissenschaften.* **49**, 1962, 156.
34. de Jong IG, Wiles DR. Studies on the pentacarbonyltechnetium radical. *Inorg. Chem.* **12**, 1973, 2519-2522.
35. Ferradini C, Carlier R, Genet M, et al. Chemical effects associated with β -emission. III. Technetium-99m formed by the β -disintegration of molybdenum-99. *Radiochim. Acta* **12**, 1969, 1-4.
- 36a. Tucker WD, Greene MW, Weiss AJ, et al. BNL-3746, Brookhaven Nat'l. Lab, Upton, New York, 1958.
- 36b. Richards, P. A survey of the production at Brookhaven Nat'l Lab. of radioisotopes for medical research. *Trans. 5th Nuclear Congress, 7th Int. Electronic Nuclear Symposium (Rome)*, June, 1960, 255.
37. Cotton FA, Wilkinson G. *Advanced Inorganic Chemistry*, 5th ed. Wiley-Interscience, New York, 1988, 812.
38. Cotton FA, Wilkinson G. *Advanced Inorganic Chemistry*, 5th ed. Wiley-Interscience, New York, 1988, 817.
39. Lebedeva LI and Kyong K. Interaction between phosphorous(V), molybdenum(VI) and aluminum(III) in weak acid solutions. *Vestnik Leningrad Univ.* **23**, 1968, 127-131.
40. Duca A, Budiu T. Determination of the instability constant of the phospho-12-molybdic acid by means of the paper chromatographic method. *Rev. Roum. Chim.* **11**, 1966, 585-589.
41. Millman WS, Crispin M, Cirillo WS, et al. Studies of the hydrogen held by solids. XXII. The surface chemistry of reduced molybdena-alumina catalysts. *J. Catal.* **60**, 1979, 404.

42. Wefers K, Bell GM. Oxides and hydroxides of aluminum. Technical Paper, Alcoa Res. Lab. No. 19, 1972, 51.
43. Brockmann H, Schodder H. Aluminum oxide with buffered adsorptive properties for purposes of chromatographic adsorption. Ber. Deutsch. Chem. Ges. B74, 1941, 73-78.
44. Lederer M, Polcaro C. Thin-layer chromatography of inorganic anions on aluminum oxide. J. Chromatogr. 84, 1973, 379-386.
45. United States Pharmacopoeia (XXII), 1989 p. 600
46. United States Pharmacopoeia (XXII), 1989, p. 1318
47. Cifka J., Vesely P. Some factors influencing the elution of technetium-99m generators. Radiochim. Acta 16, 1971, 30-35.
48. Abrashkin S, Heller-Grossman L, Schafferman A, et al. Technetium-99m generators: the influence of the radiation dose on the elution yield. Int. J. Appl. Radiat. Isot. 29, 1978, 395-399.
49. Draganic IG, Draganic ZD. The radiation chemistry of water. Academic Press, New York, 1971. Chapters 2,3 and 4.
50. Pikaev AE, Kryuchkov SV, Kuzina AF, et al. Pulsed radiolysis of neutral aqueous solutions of potassium pertechnetate. Dokl. Akad. Nauk. SSSR 236, 1977, 1155-1158. (English Transl.)
51. Deutsch E, Heineman WR, Hurst R, et al. Production, detection and characterization of transient hexavalent technetium in aqueous alkaline media by pulse radiolysis and very fast scan cyclic voltammetry. J. Chem. Soc., Chem. Commun. 1978, 1038-1040.
52. Boyd RE. Recent developments with generators of 99mTc, in Radiopharmaceuticals and Labelled compounds, Vol. I, IAEA, Vienna, 1973, M. 3-26.
53. Steigman J. Chemistry of the alumina column. Int. J. Appl. Radiat. Isot. 33, 1982, 829-834.
54. Reiche H, Dunn WW, Bard AJ. Heterogeneous photocatalytic and photosynthetic deposition of copper on titanium dioxide and tungsten (VI) oxide powders. J. Phys. Chem. 83, 1979, 2248-2251.
55. Pettus C. Molybdenum oxide: negative resistance device. IEEE Proceedings 53, 1965, 98.
56. Colton RJ, Guzman AM, Rabalais JW. Photochromism and electrochromism in amorphous transition metal oxide films. Acc. Chem. Res. 11, 1978, 170-176.
57. Levin VI, Kozyreva-Alexandrova LS, Sokolova TN, et al. A new technetium-99m generator of higher activity. Int. J. Appl. Radiat. Isot. 30, 1979, 450-451.
58. Charlton JC and Lyons D. German patent 2,238, 503 (Feb. 22, 1973).
- 58a. Salehi N, Guignard PA. Milking techniques of 99m generators and labeling efficiencies. Int. J. Appl. Radiat. Isot. 36, 1985, 417-418.
- 58b. Deutsch E, Heineman WR, Zodda JP, et al. Preparation of "no-carrier-added" Technetium-99m complexes: determination of the total Technetium content of generator eluents. Int. J. Appl. Radiat. Isot. 33, 1982, 843-848.

- 58c. Srivastava SC, Meinken G, Smith TD, et al. Problems associated with stannous ^{99m}Tc radiopharmaceuticals. *Int. J. Appl. Radiat. Isot.* 28, 1977, 83-95.
- 58d. Smith TD, Richards P. A simple kit for the preparation of ^{99m}Tc -labeled red blood cells. *J. Nucl. Med.* 17, 1976, 126-132.
- 58e. Bayne VJ, Forster AM, Tyrrell DA. Use of sodium iodide to overcome the eluate age restriction for Ceretec reconstitution. *Nucl. Med. Comm.* 10, 1989, 29-33.
- 58f. Molinski VJ. A review of ^{99m}Tc generator technology. *Int. J. Appl. Radiat. Isot.* 33, 1982, 811-819.
- 58g. Hamilton G. Contamination of contrast agent by MBT in rubber seals. *Can. Med. Assoc. J.* 136, 1987, 1020.
- 58h. Boyd RE, Sorby PJ. Improved elution efficiency of ^{99m}Tc generators following purification of the eluting saline. *Int. J. Appl. Radiat. Isot.* 35, 1984, 993-994.
59. Kuzina AF, Tagil TS, Zamosanikova NN, et al. Extraction of technetium-99 with acetone. *Dokl. Akad. Nauk SSSR* 145, 1962, 106-108; *Proc. Acad. Sci. USSR Chem. Sec.* 142/147, 1962, 569-571.
60. Gemmill WJ, King PA, Molinski VJ. Production of a solution containing radioactive technetium. U.S. Patent No. 3436354, 1969.
61. Tachimori S, Nakamura H, Amano H. Preparation of technetium-99m by direct adsorption from organic solution. *J. Nucl. Sci. Technol.* 8, 1971, 357-362.
62. Boyd RE. Technetium-99m generators- the available options. *Int. J. Appl. Radiat. Isot.* 33, 1982, 801-809.
63. Krebs B, Hasse KD. Refinements of the crystal structures of potassium pertechnetate, potassium perrhenate, and osmium tetroxide. The bond lengths in tetrahedral oxo-anions and oxides of d^0 transition metals. *Acta Crystallogr. Sect. B*, 32, 1976, 1334-1337.
64. Mayfield HG, Bull WE. Perrhenato complexes of bivalent cations. *Inorg. Chim. Acta.* 3, 1969, 676-680.
65. Macasek F. Coextraction of technetium with uranyl nitrate tributylphosphate complex. *Radiochem. Radioanal. Lett.* 22, 1975, 175-183.
66. Majumdar SK, Pacer RA, Rulfs CL. Rhenium and technetium (VI) and meso-(VII) species. *J. Inorg. Nucl. Chem.* 31, 1969, 33-41.
67. Steigman J, Gerber R, Hwang LL-Y. Polyhydroxy complexes of rhenium (VII). *J. Inorg. Nucl. Chem.* 41, 1979, 863-866.
- 68a. Vajo J J, Aikens DA, Ashley L, et al. Facile electroreduction of perrhenate in weakly acidic citrate and oxalate media. *Inorg. Chem.* 20, 1981, 3328-3333.
- 68b. Russell CD, Cash AG. Polarographic reduction of pertechnetate. *J. Electroanal. Chem.* 92, 1978, 85-99.

69. Boyd GE. Osmotic and activity coefficients of aqueous pertechnetate acid and perhenic acid solutions at 25°C. *Inorg. Chem.* 17, 1978, 1808-1810.
- 70a. Tribalat S, Beyden J. Isolation of technetium. *Anal. Chim. Acta* 8, 1953, 22-28.
- 70b. Boyd GE, Larsen QV. Solvent extraction of septivalent technetium. *J. Phys. Chem.* 64, 1960, 988-996.
- 71a. Atteberry, RW, Boyd GE. Separation of seventh group anions by ion-exchange chromatography. *J. Am. Chem. Soc.* 72, 1950, 4805-6.
- 71b. Boyd GE, Larsen QV, Motta EE. Isolation of milligram quantities of long-lived technetium from neutron irradiated molybdenum. *J. Am. Chem. Soc.* 82, 1960, 809-815.
72. Diamond RM. The aqueous solution behavior of large univalent ions. A new type of ion - pairing. *J. Phys. Chem.* 67, 1963, 2513-2517.
73. Hayes M, Green FA. Binding of $^{99m}\text{TcO}_4^-$ by human serum and tissues. *J. Nucl. Med* 12, 1971, 365.
74. Hays MT, Green FA. In vitro studies of technetium - ^{99m} - labeled pertechnetate binding by human serum and tissues. *J. Nucl. Med* 14, 1973, 149-158.
75. Kominami G, Yokoyama A, Kikumoto S, et al. Pertechnetate binding to human serum albumin. *Radioisotopes (Tokyo)* 26, 1977, 234-237.
76. Scatchard G. The attraction of proteins for small molecules and ions. *Ann. N.Y. Acad. Sci* 51, 1949, 660-672.
77. Kominami G, Yokoyama A, Tanaka H. The pertechnetate ion binding to human serum albumin - the competition with other anions. *Radioisotopes (Tokyo)* 26, 1977, 525-529.
78. Scatchard G, Coleman JS, Shen AL. Physical chemistry of protein solutions. VII. The binding of some small anions to serum albumin. *J. Am Chem. Soc.* 79, 1957, 12-20.
79. Johannsen B, Berger R, Schumacher K. The binding of technetium compounds by human serum albumin. *Radiochem Radioanal Lett.* 42, 1980, 177-188
80. Dewanjee MK, Brueggemann P, Wahner HW. Affinity constants of technetium-99- pertechnetate and technetium-chelates with human serum albumin. *Radiopharmaceuticals II*, 2nd International Symp. Society of Nuclear Medicine. 1979, 435-447.
81. Rulfs CL, Meinke WW. Observations on some chemical and physical properties of technetium and its compounds. *J. Am. Chem. Soc.* 74, 1952, 235-236.
82. Boyd GE, Larson QV, Motta EI. Isolation of milligram quantities of long-lived technetium from neutron-irradiated molybdenum. *J. Am. Chem. Soc.* 82, 1960, 809-815.
83. Harper PV, Lathrop KA, Richards P. Tc^{99m} as a radiocolloid. *J. Nucl. Med.* 5, 1964, 382.
84. Garzon OL, Palcos MC, Radicella R. Technetium- ^{99m} labeled colloid. *Int. J. Appl. Radiat. Isotopes* 16, 1965, 613.

85. Pauli WO, Kolbl LW, Laub A. The synthesis of highly purified sulfur sols. II. The antimony sulfide sol. *Kolloid-Z.* 80, 1937, 175-185.
86. Pauli WO and Laub A. The synthesis of highly purified sulfur sols. I. The arsenious sulfide sol. *Kolloid-Z.* 78, 1937, 295-306.
87. Schuessler HD, Herrmann G. Rapid exchange of metal ions on metal sulfide cellulose. *Radiochim Acta* 13, 1970, 65-69.
88. Zuber G, Liser KH. Selective separation of technetium. *Radiochim Acta* 21, 1974, 60-62.
89. Atkins HL, Richards P, Schieffer L. Scanning of liver, spleen, and bone marrow with colloidal 99m technetium. *Nucl. Applic.* 2, 1966, 27.
90. Stern HS, McAfee JG, Subramanian G. Preparation, distribution and utilization of technetium-99m -sulfur colloid. *J. Nucl Med* 7, 1966, 665-675.
91. Cifka J, Vesely P. Non-per technetate radiochemical impurity in sulfur colloid labeled with technetium-99m. Chemical study of the labeling process. *Radiopharm. Label. Compounds*, Proc. Symp. 1, 53-62, IAEA, Vienna, 1973.
92. The lower oxy-acids of sulfur, by D. Lyons and G. Nickless, in *Inorganic Sulfur Chemistry*, G Nickless, ed., Elsevier Publishing Company, 1968, 529-530.
93. Briscoe HV, Robinson PL, Stoddart EM. The sulfides and selenides of rhenium. *J. Chem. Soc.*, 1931, 1439-1443.
94. Dowson WM, Jones WF. Qualitative Inorganic Analysis. Part XLIII. Alkali metal salts of the sulfur oxyacids. *Mikrochim. Acta*, 1974, 339-368.
95. Steigman J, Solomon NA, Hwang LL-Y. Technetium - sulfur colloid. *Int. J. Appl. Radiat. Isot.* 37, 1986, 223-229.
96. Davis MA Jones AG, Trindade H. A rapid and accurate method for sizing colloids. *J. Nucl Med* 15, 1974, 923-928.
97. Zaiser EM, LaMer VK. The kinetics of the formation and growth of monodispersed sulfur hydrosols. *J. Colloid Sci.* 3, 1948, 571-578.
98. Handbook of Chemistry and Physics, 59th edition. CRC Press Inc. West Palm Beach, Florida, D-203, 1978-1979, D-203.
99. Cohen MB. Reducing particle size in ^{99m}Tc-sulfur colloid preparations. *J. Nucl. Med.* 11, 1970, 767.
100. Müller A, Krebs B, Diemann EZ. The reaction of per technetate and rhenate with hydrogen sulfide. Formation of tetrathionatoperrhenate ions in solution. *Zeit. Anorg. Allgem. Chem.* 353, 1967, 259-264.
101. Cartledge GH, Smith WT. Revision of the electrode-potential diagram for technetium. *J. Am. Chem. Soc.* 59, 1955, 1111-1112.

102. Cobble JW, Smith WT, Boyd GE. Thermodynamic properties of technetium and rhenium compounds. II. Heats of formation of technetium heptoxide and pertechnic acid, potential of the technetium (IV)-technetium (VII) couple, and a potential diagram for technetium. *J. Am Chem. Soc.* 75, 1952, 5777-5782.
103. Liebecher L, Muenze R. Determination of the standard potential for the $\text{TcO}_4/\text{TcO}_2 \times \text{H}_2\text{O}$ half cell. *Zentralinst. Kernforsch., Rosendorf Dresden*, 1975, 140-143.
104. Spitsyn VI, Kuzina AF, Zamosanikova NN, et al. Chemical and electrochemical behavior of technetium in aqueous solutions. *Proc. Intern. Conf. Peaceful Uses At. Energy*, 3rd, Geneva, 10, 1964, 561-570.
105. The oxidation states of the elements and their potentials in aqueous solutions by Latimer WM, 2nd edition, 1953, Prentice-Hall Inc., NY, 243.
106. Mager RJ, Blustein H. Section on technetium and rhenium in *Standard Potentials in Aqueous Solution*, IUPAC Bard AJ, Parson R and Jordon J. eds, Marcel Dekker Inc. NY & Basel, 1985, 436.
107. Donaldson JD, Moser W. Pure tin (II) sulfate. *J. Chem Soc.*, 1960, 4000-4003.
108. Abel E. Is autooxidation catalyzed by chloride ion? *Monatsh* 85, 1954, 949-956.
109. Donaldson JD, Moser W, Simpson WB. Tin (II) acetates *J. Chem. Soc. (suppl)*, 1964, 5942-5947.
110. Tobias RS. Studies on the hydrolysis of metal ions, 21. The hydrolysis of tin(II) ion, Sn^{2+} , *Acta Chem. Scand.* 12, 1958, 198-223.
111. Vanderzee CE, Rhodes DE. Thermodynamic data on the stannous chloride complexes from electromotive force measurements. *J. Am. Chem. Soc.* 74, 1952, 3552-3555.
112. Gobom S. The hydrolysis of the tin(II) ion. *Acta Chem. Scand. Ser. A* 30, 1976, 745-750.
113. Donaldson JD, Moser W, Simpson WB. Basic tin (II) chloride. *J. Chem. Soc.* 1963, 1727-173.
114. Donaldson JD, Moser W. Hydrous tin oxide. *J. Chem. Soc.* 1961, 835-838.
115. The oxidation states of the elements and their potentials in aqueous solutions by Latimer WM, 2nd edition, 1953, Prentice-Hall Inc., NY, 148-150.
116. Cotton FA, Wilkinson G. *Advanced Inorganic Chemistry*, 3rd ed. Wiley-Interscience, New York, 1972, 331.
117. Bishop E, Hitchcock PH. Mass and charge transfer kinetics and coulometric current efficiencies. *Analyst* 98, 1973, 635-646.
118. Forbes GS, Bartlett EP. The measurement of oxidation potentials at mercury electrodes. I. The stannic-stannous potential. *J. Am Chem. Soc.* 36, 1914, 2030-2040.
119. Sykes AG. Further advances in the study of mechanisms of redox reactions in *Advances in Inorganic Chemistry and Radiochemistry*, Emeléus HJ and Sharpe AG eds, Academic Press, New York, 1967, vol. 10, 153-245.

120. Shaffer PA. Reaction velocity and the "equi-valence-change principle". J. Am. Chem. Soc. 55, 1933, 2169-2170.
121. Cotton FA, Wilkinson G. Advanced Inorganic Chemistry, 3rd ed. Wiley-Interscience, New York, 1972, 679.
122. Shinohara N, Mori K, Inoue M. Aqueous chemistry of tin (III). A flash photolysis study, Chem. Lett. 5, 1986, 661-664.
123. Higginson WCE, Leight RT, Nightingale R. Reducing reactions of tin (II) in aqueous solution. I. A method for the detection of tin (III). J. Chem. Soc., 1962, 435-439.
124. Drye DJ, Higginson WCE, Knowles P. Reducing reactions of Sn (II) in aqueous solution. II. The reaction between Sn (II) and (IV) in dilute HCl. J. Chem. Soc. 1962, 1137-1143.
125. Wetten EAM, Higginson WCE. Reducing reactions of tin (II) in aqueous solution. Part III. The reduction of various common oxidising agents. J. Chem. Soc. 1965, 5890- 5906.
126. Cotton FA, Wilkinson G. Advanced Inorganic Chemistry, 3rd ed. Wiley-Interscience, New York, 1972, 673-675.
127. Duke FR, Pinkerton RC. The rôle of halide ions in the ferric-stannous reaction. J. Am. Chem. Soc. 73, 1951, 3045-3049.
128. Duke FR, Peterson NC. The tin (II) reduction of methyl orange. J. Phys. Chem. 63, 1959, 2076-2077.
129. Haight Jr. GP, von Frankenberg C. The molybdenum-catalyzed reduction of hydroxylamine with stannous chloride. Acta Chem. Scandinav. 15, 1961, 2026-2036.
130. Cotton FA, Wilkinson G. Advanced Inorganic Chemistry, 3rd ed. Wiley-Interscience, New York, 1972, 330.
131. Donaldson JD. Progress in Inorganic Chemistry, Colton FA ed, Chemistry of bivalent tin. Interscience Publishers, New York, Vol. 8, 1967, pp. 326-329.
132. Deutsch E, Elder RC, Large BA, et al. Structural characterization of a bridged technetium-99- tin-dimethylglyoxime complex: Implications for the chemistry of technetium-99-labeled radiopharmaceuticals prepared by the tin (II) reduction of pertechnetate. Proc. Nat'l Acad. Sci. U.S.A. 73, 1976, 4287-4289.
133. Steigman J, Meinken G, Richards P. The reduction of pertechnetate-99 by stannous chloride II. The stoichiometry of the reaction in aqueous solutions of several phosphorus (V) compounds. Int. J. Appl. Radiat. Isot. 29, 1978, 653-660.
134. Tofe AJ, Francis MD. Optimization of the ratio of stannous tin: ethane-1-hydroxy-1, 1-diphosphonate for bone scanning with ^{99m}Tc-pertechnetate. J. Nucl. Med. 15, 1974, 69-74.
135. Van den Brand JAGM. Technetium (tin) ethane-1-hydroxy-1,1-diphosphonate complexes: preparation, composition and biodistribution. ECN-98, Netherlands Energy Research Foundation, 1755 ZG Petten (NH 1), The Netherlands, October, 1981.

136. Mikelsons MV, Pinkerton TC. Liquid chromatography of tin-reduced technetium hydroxyethylidene diphosphonate complexes for on-line spectral characterization and double isotope labeling. *Anal. Chem.* 58, 1986, 1007-1013.
137. Loberg MD, Fields AT. Chemical structure of technetium-99m-labeled N-(2,6-dimethylphenylcarbamoylmethyl)-iminodiacetic acid (^{99m}Tc -HIDA). *Int. J. Appl. Radiat Isot.* 29, 1978, 167-173.
138. Steigman J, Hwang L.L.-Y, Solomon NA. (Unpublished)
139. Smith TD. Chelates formed by tin (II) with citric and tartaric acids, and their interaction with certain transition-metal ions. *J. Chem. Soc.*, 1965, 2145-2150.
140. Subramanian G, McAfee JG. Use of sodium borohydride in labeling biologically useful compounds with ^{99m}Tc . *J. Nucl. Med.* 10, 1969, 443.
141. Brown HC, Krishnamurthy S. Forty years of hydride reductions. *Tetrahedron* 1979, 567-607.
142. Brown HC, Schlesinger HI, Finholt AE et al. Sodium borohydride, its hydrolysis and its use as a reducing agent and in the generation of hydrogen. *J. Am. Chem. Soc.* 75, 1953, 215-219.
143. Pojer PM, Spokas RJ. Reduction of Per technetate [^{99m}Tc] by transition metal "Borides". *Nucl. Med. Commun.* 3, 1982, 145-149.
144. Davis RE, Bromels E, Kibby CL. Boron Hydrides. III. Hydrolysis of sodium borohydride in aqueous solution. *J. Am. Chem. Soc.* 84, 1962, 885-892.
145. Willem R. Possible mechanisms of the reaction between tetrahydroborate and hydrogen ions: a permutational analysis. *J. Chem. Soc. Dalton Trans.*, 1979, 33-40.
146. Olah GA, Klopman and Schlosberg. Chemistry in super acids. III Protonation of alkanes and the intermediary of alkonium ions, pentacoordinated carbon cations of the CH_5^+ type, etc. *J. Am. Chem. Soc.* 91, 1969, 3261-3268.
147. Talroze VL, Lyubimova AK. Secondary processes in the ion source of the mass spectroph. *Dokl. Akad. Nauk SSSR* 86, 1952, 909-912.
148. Field FH, Munson MSB. Reactions of gaseous ions. XIV. Mass spectrometric studies of methane at pressures to 2 Torr. *J. Am. Chem. Soc.* 87, 1963, 3289-3294.
149. Pacer RA. Borohydride reduction of the perhenate ion. *J. Inorg. Nucl. Chem.* 35, 1973, 1375-1377.
150. Pacer RA. Borohydride reduction of pertechnetate ion. *J. Inorg. Nucl. Chem.* 38, 1976, 817-818.
151. Steigman J, Hwang LL-Y, Aronson F. (Unpublished)
152. Burns HD, Worley, Wagner HN et al in *The Chemistry of Radiopharmaceuticals*, Heindel ND. Burns HD, Honda T, et al, eds. Masson Publishing USA Inc., New York, 1978, 279-280.
153. Cotton FA, Wilkinson G. *Advanced Inorganic Chemistry*, 3rd ed. Wiley-Interscience, New York, 1988, 451.

154. Jones AG, Orvig C, Trop HS, et al. A survey of reducing agents for the synthesis of tetraphenylarsonium oxotechnetiumbis (ethanedithiolate) from [⁹⁹Tc] pertechnetate in aqueous solution. *J. Nucl. Med.* 21, 1979, 279-281.
155. Latimer WM. *Oxidation Potentials*, 2nd edition, Prentice Hall, New York, 1952, 109.
156. Van Wazer JR, *Phosphorus and its Compounds*, John Wiley New York, 1966, Vol. I, 351.
157. Cotton FA, Davison A, Day VW. Preparation and structural characterization of salts of oxotetrachlorotechnetate (V). *Inorg. Chem.* 18, 1979, 3024-3029.
158. Busey RM. Chemistry of technetium in hydrochloric acid solution, U.S. Atomic Energy Commission Doc. ORNL 2782, Oak Ridge Nat'l Lab, Tenn, 1959, 13.
159. Jezowska-Trezbiatowska, Baluka M. Oxychlorotechnetate(V). *Bull. Acad. Polon. Sci. Serv. Sci. Chem.* 13, 1965, 1-4.
160. Schwochau K, Hedwig, Schenk HJ, Greis O. Identification and properties of dinegative octachloroditechnetate(III). *Inorg Nucl. Chem. Lett.* 13, 1977, 77-80.
161. Cotton FA, Daniels L, Davison A, et al. Structural characterization of the octachloroditechnetate (III) ion in its tetra-n-butylammonium salt. *Inorg. Chem.* 20, 1981, 3051-3055.
162. Cotton FA, Wilkinson G. *Advanced Inorganic Chemistry*, 3rd ed. Wiley-Interscience, New York, 1972, 35.
163. Adams JQ, Thomas JR. Electron paramagnetic resonance (E.P.R.) of a hydrazine radical ion. *J. Chem. Phys.* 39, 1963, 1904-1906.
164. Tolbert B, Downing M, Carlson RW, et al. Chemistry and metabolism of ascorbic acid and ascorbate sulfate. *Annals NY Acad. Sci* 258, 1975, 55-65.
165. Ball E.G. Studies on oxidation-reduction. XXIII. Ascorbic acid. *J. Biol. Chem.* 118, 1937, 219-239.
166. Khan MMT, Martell AE. Metal ion and metal chelate- catalyzed oxidation of ascorbic acid by molecular oxygen. I. Cupric and ferric ion- catalyzed oxidation. *J. Am Chem. Soc.* 89, 1967, 4176-4185.
167. Michaelis L. Theory of the reversible two-step oxidation. *J. Biol. Chem.* 96, 1932, 703-715.
168. Bielski BHJ. Chemistry of ascorbic acid radicals in *Advances in Chemistry Series*, No 200, Ascorbic Acid Chemistry, Metabolism and Uses. Seib PA and Tolbert BM Editors, American Chemical Society, 1982, 81-100.
169. Pelizzetti E, Meisel D, Mulac WA, et al. On the electron transfer from ascorbic acid to various phenothiazine radicals. *J. Am. Chem. Soc.* 101, 1979, 6954-6959.
170. Laroff GP, Fessenden RW, Schuler RH. Electron spin resonance spectra of radical intermediates in the oxidation of ascorbic acid and related substances. *J. Am. Chem. Soc.* 94, 1972, 9062-9073.

171. Weissberger A, LuValle JE. Oxidation Processes. XVII. The autoxidation of ascorbic acid in the presence of copper. *J. Am. Chem. Soc.* 66, 1944, 700.
172. Yokoyama A, Kominami G, Hirada S, et al. The role of ascorbic acid with the ferric ion in labeling human serum albumin with Technetium-99m. *Int. J. Appl. Radiat. Isot.* 26, 1975, 291-299.
173. Stern HS, McAfee JG, Zolle, I. Technetium-99m-albumin. *AEC Symp. Series 6*, 1966, 352-382.
174. Marx G, Chevon M. Site -specific modification of albumin by free radicals. Reaction with copper (II) and ascorbate. *Biochem. J.* 236, 1986, 397-400.
175. Clark WM. Oxidation-Reduction Potentials of Organic Systems. The Williams and Wilkins Co., Baltimore Md, 1960, 471-487.
176. Gilbert BC, Norman ROC, Placucci G, et al. Electron spin resonance studies. Part XLV. Reactions of the methyl radical with some aliphatic compounds in aqueous solution. *J. Chem. Soc. Perkin II*, 1975, 892-900.
177. Kertesz JC, Wolf MB, Wolf W, et al. Electron spin resonance studies of free radicals in solution III: pH dependence of thyl free radical cysteine. *J. Pharm. Sci.* 63, 1974, 880.
178. Latimer WM: Oxidation Potentials, 2nd edition. Prentice-Hall, Inc. New York, 1952, 223, 248 and 294.
179. Latimer WM: Oxidation Potentials, 2nd edition. Prentice-Hall, Inc. New York, 1952, 44, 74.
180. Higginson WCE, Marshall JW. Equivalence changes in oxidation-reduction reactions in solution: some aspects of the oxidation of sulfurous acid. *J. Chem. Soc.* 1957, 447-458.
181. Halperin J, Taube H. The transfer of oxygen atoms in oxidation-reduction reactions. III. The reaction of halogenates with sulfite in aqueous solution. *J. Am Chem. Soc.* 74, 1952, 375-380.
182. Davison A, Jones AG, Abrams MJ. New 2,2-bipyridine and 1,10-phenanthroline oxohalide complexes of technetium (VII) and (V). *Inorg. Chem.* 20, 1981, 4300-4302.
183. Grove DE Johnson NP, Wilkinson G. Trioxotrichlororhenate (VII) ion. *Inorg. Chem.* 8, 1969, 1196-1199.
184. Aronson FL, Hwang L L-Y, Ronca N, Solomon NA, Steigman J. Formation and stabilization of anionic metal complexes in concentrated aqueous quaternary ammonium salt solutions. *Inorg. Chem.* 24, 1985, 541-545.
185. Fritzberg AR, Lyster DM, Dolphin DH. Evaluation of formamidine sulfinic acid and other reducing agents for use in the preparation of Tc-99m labelled radiopharmaceuticals. *J. Nucl. Med.* 18, 1977, 553-557.
186. McGill JE, Lindstrom F. Mechanism of reduction of cadmium by aminoiminomethanesulfinic acid in alkaline media. *Anal. Chem.* 49, 1977, 26-29.
187. Shashoua VE. Formamidine sulfinic acid as a biochemical reducing agent. *Biochem.* 3, 1964, 1719-20.

188. Latimer WM. Oxidation Potentials, 2nd Edition. Prentice-Hall, Inc., New York, 1952, 168.
189. Latimer WM. Oxidation Potentials, 2nd edition. Prentice-Hall, Inc. New York, 1952, 172.
190. Nazer AFM, Wells CF: Kinetics and mechanism of the oxidation of hydroxylamine by aquovanadium (V) ions in aqueous perchlorate media. *J. Chem. Soc.* 93, 1971, 5892.
191. Simic M, Hayon E. Intermediates produced from the one-electron oxidation and reduction of hydroxylamines. Acid-base properties of the amino, hydroxyamino and methoxyamino radicals. *J. Am. Chem. Soc.* 93, 1971, 5982.
192. Gutch CJW, Waters WA. The electron spin resonance spectra of some hydroxylamine free radicals. *J. Chem. Soc.*, 1965, 751-755.
193. Wells CF, Mays D. The kinetics of the oxidation of hydrazoic acid by Co III aq. *J. Inorg. Nucl. Chem.* 33, 1971, 3855-3859.
194. Brown JK, Fox D, Heyward MP, Wells Cecil F. Kinetics of oxidation of hydrogen azide (hydrazoic acid) by tris (2, 2'-bipyridyl) nickel (III) ions in aqueous perchlorate media: comparison with oxidation by aquocations. *J. Chem. Soc. Dalton Trans.* 5, 1979, 735-739.
195. DeSchrijver M. Method and kit for the preparation of radiopharmaceuticals. *Swiss Appl.* 77/11,027, 08 Sept. 1977.
196. Basmadjian GP and Fitzgerald M: Abstracts of 15. Internationale Jahrestagung der Gesellschaft für Nuklearmedizin, September 1977, Groningen.
197. Camin LL, Liteplo MP, Pratt FP. Solid phase reductants for the preparation of Technetium-99m radiopharmaceuticals. *J. Labeled Comp. and Radiopharm.* 15, 1979, 24-25.
198. Ruddock CF: Method and container for reducing pertechnetates. *Brit. UK Pat. App.* 2,046,000, Nov. 5, 1980.
- 199a. Kato S, Kurata K, Ikeda I, Toshihiro S, Hiroshi A.. A simple device for preparation of various ^{99m}Tc compounds in sterilized form by an electrolytic method. *J. Nucl. Med.* 74, 1973, 415.
- 199b. Schneider PB. A simple "electrolytic" preparation of a ^{99m}Tc(Sn) citrate renal scanning agent. *J. Nucl. Med.* 14, 1973, 843-845.
200. Benjamin PP, Rajali A, Fridell H. Electrolytic complexation of ^{99m}Tc at constant current: its applications in nuclear medicine. *J. Nucl. Med.* 11, 1970, 147-154.
201. Steigman J, Eckelman WC, Menken G, Isaacs HS, Richards P. The chemistry of technetium labeling of radiopharmaceuticals by electrolysis. *J. Nucl. Med.* 15, 1974, 75-80.
202. Russell CD. Carrier electrochemistry of pertechnetate: application to radiopharmaceutical labeling by controlled potential electrolysis at chemically inert electrodes. *Int. J. Appl. Radiat and Isot.* 28, 1977, 245-249.
203. Steigman J, Chin EV, Solomon NA. Scintiphotos in rabbits made with Tc-99m preparations reduced by electrolysis and by SnCl₂-reduced Tc-99m preparations. *J. Nucl. Med.* 20, 1979, 766-770.
204. Sand HJS. The separation of metals by internal electrolysis. *Analyst* 55, 1930, 309.

205. Electrolysis vessel-polarographic H form, Sargent-Welch, Scientific Company, Skokie, Ill, Catalog 133, 1985-86, # S-29400, 410.
206. Latimer WM: Oxidation Potentials, 2nd edition. Prentice-Hall, Inc. New York, 1952, 168.
207. Latimer WM. Oxidation Potentials, 2nd edition. Prentice-Hall, Inc. New York, 1952, 170.
208. Steigman J, Ronca N, Hwang L L-Y et al. (Unpublished)
209. Banks E, Wold A. Oxide Bronzes in Preparative Inorganic Reactions, Vol. 4, W.L. Jolly ed., Interscience Publishers New York, 1968, 237-268.
210. Steigman J, Lopez C, Hwang L-LY et al. Unpublished.
211. Brisse F, Stewart DJ, Seidl V, Knop O. . Pyrochlores. VIII. 2-5 Pyrochlores and related compounds and minerals. Can. J. Chem. 50, 1972, 3648-3666.
- 211a. Risley JM, Van Etten RL. Origin of the oxygen of triphenylphosphine by potassium persulfate-application of the ¹⁸O isotope effect in ³¹P NMR. Int. J. Chem. Kinetics 16, 1984, 1167-1173.
- 211b. Phosphorus and its compounds, Vol. I, Chemistry, John K. Van Wazer, Interscience, NY 1958, 195-197.
212. Eakins JD, Humphries DG, Mellish CE. New compounds in which technetium has a low valency. J. Chem. Soc. 1963, 6012-6016.
213. Armstrong RA, Taube H. Chemistry of trans-aquanitrosyl-tetraammine technetium (I) and related studies. Inorg. Chem. 15, 1976, 1904-1909.
214. Hieber W, Nast R, Gehring G. Reductive nitrosylation of tetraoxometallates with NH₂OH in strong alkali. J. Inorg. Allg. Chem. 169, 1948, 256.
215. Bhakacharyya R and Roy, PS: Reductive nitrosylation of tetraoxometallates. Part II. Generation of [Re (NO)] moiety: A novel and virtually single step synthesis of [Re (NO) (NCS)₃ H₂O] and its 2,2'-bipyridyl and 1,10-phenanthroline derivatives directly from perrhenate in aqueous and aerobic media. Transition Metal Chem. (Weinheim, 9 er.) 7, 1982, 285-286.
216. Baldas J, Pojer PM. The use of formamidinesulfinic acid in the preparation of Tc-99m-labeled radiopharmaceuticals - a cautionary note. Aust. Radiat. Lab [Tech. Rep.] ARL/TR 1980, ARL/TR015, 8 pp.
217. Pojer PM, Baldas J. Technetium-99m-labeled N,N-diethyldithio carbamate-a non-polar complex with slow hepatic clearance. ARL/TR 1980, ARL/TR 025, 6 pp.
218. Baldas J, Pojer PM. The use of formamidine sulfinic acid in the preparation of Tc-99m-labeled radiopharmaceuticals - a cautionary note. Int. J. Nucl. Med. Biol. 8, 1981, 110-111.
- 219a. Baldas J, Bonnyman J, Pojer PM, William GA. The influence of reducing agents on the composition of technetium-99 complexes: implications for ^{99m}Tc-radiopharmaceutical preparation. Aust. Radiat. Lab. [Tech. Rep.] ARL/TR 1981, ARL/TR 033, 8pp.

- 219b. Baldas J, Bonnyman J, Pojer PM, William GA. The influence of reducing agents on the composition of technetium-99 complexes: implications for ^{99m}Tc -radiopharmaceutical preparation. *Eur. J. Nucl. Med.* 7, 1982, 187-189.
220. Baldas J, Bonnyman J, Pojer PM, Williams GA, Mackay MF. Preparation and crystal structure of carbonyltris (diethyldithiocarbamate) technetium (III): an unexpected source of coordinated carbon monoxide. *J. Chem. Soc. Dalton Trans.* 1982, 451-455.
221. Baldas J, Bonnyman J, Pojer PM, Williams GA, Mackay MF. Synthesis and structure of bis (diethyldithiocarbamate) nitridotechnetium (V): a technetium-nitrogen triple bond. *J. Chem. Soc., Dalton Trans.* 1981, 1798-1801.
222. Baldas J, Boas JF, Bonnyman J, Williams GA. Studies of technetium complexes. Part 6. The preparation, characterisation and electron spin resonance spectra of salts of tetrachloro- and tetrabromo-nitridotechnetate (VI). *J. Chem. Soc. Dalton Trans.* 1984, 2395-2400.
223. Steigman I, Williams H P and Solomon NA: The importance of the protein sulfhydryl group in HSA labelling with Technetium-99m. *J. Nucl. Med.* 16, 1975, 573.
224. Steigman J, Hwang L L-Y, Solomon NA. (Unpublished)
225. Steigman J, Feageson E. (Unpublished)
226. Gerlit JB. Some chemical properties of technetium. *Proc. Int. Conf. Peaceful Uses of Atomic Energy, Geneva (U.N.)*, Vol. X, 1955, 145-151.
227. Rulfs CL, Pacer RA, Hirsch RF. Technetium chemistry, oxidation states and species. *J. Inorg. Nucl. Chem.* 29, 1967, 681-691.
228. Astheimer L, Schwochau K. Electrochemical reduction of tetraoxomanganate(VII), -technetate(VII) and -rhenate(VII) in organic solvents. Preparation of tetraoxomanganate(VI), technetate(VI) and -rhenate(VI). *J. Inorg. Nucl. Chem.* 38, 1976, 1131-1134.
229. Astheimer L, Hauck J, Schenk HJ, et al. Tetraoxo anions of hexavalent technetium and rhenium. *J. Chem. Phys.* 63, 1975, 1988-1991.
230. Kissel G, Feldberg SW. Disproportionation of the technetate ion in aqueous alkaline media on electrochemical study. *J. Phys. Chem.* 73, 1969, 3082-3088.
231. Libson K, Sullivan JC, Mulac WA, et al. Pulse radiolysis studies on perrhenate and pertechnetate in aqueous media. *Inorg. Chem.* 28, 1989, 375-377.
232. Lawrence GA, Sangster DF. Pulsed radiolysis of perrhenate in neutral aqueous solution: Comparison with pertechnetate. *Polyhedron* 4, 1985, 1095-1096.
233. McLeverty JA. *Progress in Inorganic Chemistry*. F. A. Cotton ed., V. 10, John Wiley & Sons, Inc., NYC, 1968, 136-170.
234. Eisenberg R, Ibers JA. Trigonal Prismatic Coordination. The Crystal and Molecular Structure of Tris (cis-1,2-diphenylethene-1,2-dithiolato) rhenium *Inorg. Chem.* 5, 1964, 411-416.
235. Jorgensen CK. Oxidation numbers and oxidation states. Springer-Verlag, Berlin, 1969, 154.
236. Greenwood NN, Earnshaw A. *Chemistry of the Elements*. Pergamon Press, 1984, 1227.

237. Gardner JK, Pariyadth N, Corbin JL, Stiefel EI. Molybdenum and rhenium complexes of aromatic aminethiolate ligands. *Inorg. Chem.* 17, 1978, 897-904.
238. Miller FJ, Thomason PF. Spectrophotometric determination of technetium with toluene-3,4-dithiol. *Anal. Chem.* 33, 1961, 404-406.
239. Kawishima M, Koyama M, Fujinaja T. Electron transfer reactions and the nature of the solvent effect on tris-toluen-3,4-dithiolates of rhenium, tungsten, molybdenum and technetium. *J. Inorg. Nucl. Chem.* 38, 1976, 801-805.
240. Johannsen B and Spies H: Technetium Verbindungen-Chemische and radiopharmakologisch untersuchungen unter besonder Berücksichtigung von Technetium- Thio Komplexen, Akademie der Wissenschaften der DDR, Zentralinstitut für Kernforschung. DDR-8051 Dresden Deutsche demokratische Republik, Rossendorf, 1981, 122-134.
241. Stiefel EI, Eisenberg R, Rosenberg RC, Gray HB. Characterization and electronic structures of six-coordinate trigonal -prismatic complexes. *J. Am. Chem. Soc.* 88, 1966, 2956-2966.
242. Baldas J, Boas J, Bonnyman J, Mackay MF, Williams GA. Structural studies of technetium complexes. III. The crystal structure of tris [2-amino benzenethiolato (2-)-S,N] technetium (VI): a trigonal prismatic technetium geometry. *Aust. J. Chem.* 35, 1982, 2413-2422.
243. Baldas J, Boas JF, Bonnyman J, Pilbrow JR, Williams GA. Electron spin resonance study of tris [2-aminobenzenethiolato (2-)-S, N] technetium (VI) and -rhenium (VI) chelates: evidence for molecular aggregation in solution. *J. Am. Chem. Soc.* 107, 1985, 1886-1896.
244. Baldas J, Boas J, Bonnyman J, Williams GA. Studies of technetium complexes. Part 6. The preparation, characterization and electron spin resonance spectra of salts of tetrachloro- and tetrabromonitrido-technetate (VI): crystal structure of tetraphenylarsonium tetrachloronitridotechnetate (VI). *J. Chem. Soc., Dalton Trans.* 1984, 2395-2400.
- 245a. Baldas J, Bonnyman J. Substitution Reactions of $^{99m}\text{Tc NCl}_4$: a route to a new class of ^{99m}Tc -radiopharmaceuticals. *Int. J. Appl. Radiat. Isotopes* 36, 1985, 133-139.
- 245b. Thomas RW, Hceg MJ, Elder RC et al Structural (EXAFS) and Solution Equilibrium Studies on the Oxotechnetium(V) Complexes TcOx_4^- and TcOX_5^{2-} (X = Cl, Br). *Inorg. Chem.* 24, 1985, 1472-1477.
- 245c. Baldas J, Boas JF An Electron Spin Resonance and Optical Study of the Behavior of $\text{Cs}_2(\text{TcNCl}_5)$ in Hydrochloric Acid Solutions. *J. Chem. Soc., Dalton Trans.*, 1988, 2585-2589.
- 245d. Baldas J, Boas JF, Bonnyman J et al Reactions of Caesium Pentachloronitridotechnetate(VI) and Nitrido-Technetate(VI) Acid. Third International Congress on Technetium, Montegrotto, Italy, August 1989.
246. Baldas J, Bonnyman J, Williams GA. Studies of technetium complexes. 9. Use of the tetrachloronitridotechnetate (VI) anion for the preparation of nitrido complexes of technetium. Crystal structure of bis (8-quinolinethiolato) nitridotechnetium (V). *Inorg. Chem.* 25, 1986, 150-153.
247. Kirmse R, Stach J. On knowledge of Pentachloro-oxo-technetate (VI), $[\text{TcOCl}_5]$. *Zeit. Für Chemie (Leipzig)*, 24, 1984, 227-228.

248. Schwochau K, Astheimer L, Hauk J, Schenk HJ. Tetraoxotechnetate (VI) and rhenate (VI). *Angew. Chem.* 86, 1974, 350-351.
249. Kirmse R, Stach J, Abram U. Pentachloronitridotechnetate (VI). $[\text{TcNCl}_5]^{2-}$ an EPR Study. *Polyhedron* 4, 1985, 1403-1406.
250. Peacock RD. in "Comprehensive Inorganic Chemistry, Vol 3, J.C. Ballar, J.H. Emelaus, R.S. Nyholm, A.F. Trotman-Dickinson, Ed., Pergamon Press, Oxford, 1973, 877-903. Elsevier Publishing Co., N.Y. 1966 quoted in DePamphilis BV, Jones AG, Davis MA et al, *J. Am. Chem. Soc.* 100, 1978, 5570-5571.
251. Rouschias G. Recent advances in the chemistry of rhenium. *Chem. Rev.* 74, 1974, 531-566.
252. Steigman J, Meinken G, Richards P. Reduction of pertechnetate-99 by stannous chloride. I. Stoichiometry of the reaction in hydrochloric acid, in a citrate buffer, and in a DTPA buffer. *Int. J. Appl. Radiat. Isot.* 26, 1975, 601-609.
253. Steigman J, Hwang L, Srivastava S. Complexes of reduced technetium-99 with polyhydric compounds. *J. Labelled Compd. Radiopharm.* 13, 1977, 160.
254. Steigman J, Hwang L, Solomon NA, Kan, Tak. Cysteine and albumin complexes of technetium-99 and technetium-99m. *J. Labelled Compd. Radiopharm.* 13, 1977, 162.
255. Kuhn CG and Isied SS: Some aspects of the reactivity of metal ion-sulfur bonds. *Prog. Inorg. Chem.*, Lippard S ed, Vol. 27, 1980, 153.
- 256a. Martell AE, Smith RM. Critical Stability Constants. Vol. 5, First Supplement, Plenum Press, NY 1982, 21.
- 256b. Martell AE, Smith RM. Critical Stability Constants, vol. IV. Inorganic Complexes, Plenum press, NMC, 1976, p 41. Thus, for $\text{Cu}^{2+} \cdot \text{NH}_3$ $\log K_1 = 4.04$, $\log K_2 = 3.43$, $\log K_3 = 2.80$, $\log K_4 = 1.48$.
257. Bunzey G, Enemark JH. Molybdenum complexes of aliphatic thiols. The structure of the syn and anti isomers of the di- μ -sulfido-bis- (sulfido-1,2-dimercaptoethanatomolybdate (V)) anion, $[\text{Mo}_2\text{S}_4(\text{S}_2\text{C}_2\text{H}_5)_2]^{2-}$. *Inorg. Chem.* 17, 1978, 682-688.
258. Johannsen B, Syhre R, Spies H, Munze R. Chemical and biological characterization of different technetium complexes of cysteine and cysteine derivatives. *J. Nucl. Med.* 19, 1978, 816-824.
259. Spies H, Johannsen B. Kinetics of reduction of pertechnetate by cysteine hydrochloride. *Zentralinst. Kernforsch. Rossendorf Dresden [Ber], ZFK-340 Jahresbericht*, 1977, 119-120.
260. Spies H, Johannsen B, Muenze R, Unverferth, K. Reaction of pertechnetate with cysteine. *Z. Anorg. Allg. Chem.* 447, 1978, 215-220.
261. Spies H, Johannsen B. Kinetic Investigations on the reaction of pertechnetate with dimercaptosuccinic acid. *React. Kinec. Catal. Lett.* 10, 1979, 153-155.
262. Chaffee E, Edwards JO. Replacement as a prerequisite to redox processes. *Progr. Inorg. Chem.*, 13, 1970, 205-242.
263. Murmann RK. The rate of oxygen exchange between the perrhenate ion and water. *J. Phys. Chem.* 71, 1967, 974-978.

264. Wiechen A, Herr W, Hess B et al. ^{18}O -Isotope Exchange between TcO_4^- and ReO_4^- Ions and Water. *Angew. Chem. Int. Ed.* **6**, 1003.
265. McCann J P, McAuley A. Metal-ion oxidations in solution. XIII. Reaction of chromium (VI) with L-cysteine in perchlorate media. *J. Chem. Soc., Dalton Trans.* 1975, 783-790.
266. Franklin KJ, Howard-Lock HE, Lock CJL. Preparation, spectroscopic properties and structure of 1-oxo-2,3,6- (D-penicillamine NSO)-4,5- (d-penicillimino-NS) Technetium (V). *Inorg. Chem.* **21**, 1982, 1941.
267. Yokoyama A, Horiuchi K, Hata N et al. Technetium in technetium -99m radiopharmaceuticals. I. Tetravalent mononuclear technetium penicillamine complex. *J. Labelled Compd. Radiopharm.* **16**, 1979, 80-81.
268. DePamphilis BV, Jones AG, Davis MA. Preparation and crystal structure of oxotechnetium bis (thiomercaptoacetate) and its relationship to radiopharmaceuticals labeled with $^{99\text{m}}\text{Tc}$. *J. Am. Chem. Soc.* **78**, 1974, 5570-5571.
269. Smith JE, Byrne EF, Colton FA, Sekutowski JC. A thiol complex of technetium pertinent to radiopharmaceutical use of $^{99\text{m}}\text{Tc}$. *J. Am. Chem. Soc.* **78**, 1978, 5571-5572.
270. Spies H, Johannsen B. Preparation and characterization of tetraethylammonium bis(1,2-dicyanoethylenedithiolato)oxo-technetate(V). *Inorg. Chim. Acta* **33**, 1979, L113.
271. Spies H, Johannsen B. Oxotechnetium (V) bis (dithiolato) complexes. *Inorg. Chim. Acta* **48**, 1981, 255-258.
272. Abram U, Spies H. Lipophilic technetium complexes. Part I. Dithiocarbamate complexes of Tc (III) and -(V). *Inorg. Chim. Acta.* **94**, 1984, L3-L6.
273. DePamphilis BV, Jones AG, Davis MA et al. Preparation of a new oxotechnetium sulfur complex radiopharm. Edited by J.A. Sorensen, Soc. Nucl. Med. Inc., New York NY, **2** Proc. Int. Symp., 2nd 1979, 155-162.
274. Brown GF, Stiefel EI. Crystal and molecular structures of bis (tetraphenylarsonium) tris (1,2-dicyanoethylenedithiolato) molybdenate (IV), $[(\text{C}_6\text{H}_5)_4\text{As}]_3[\text{Mo}(\text{mnt})_3]$, and its tungsten analog $[(\text{C}_6\text{H}_5)_4\text{As}]_3[\text{W}(\text{mnt})_3]$. *Inorg. Chem.* **12**, 1973, 2140-2147.
275. Eisenberg R, Ibers JA. Trigonal prismatic coordination: the molecular structure of Tris (cis-1,2-diphenylethene-1,2-dithiolato) rhenium. *J. Am. Chem. Soc.* **87**, 1965, 3776-3777.
276. Spies H, Johannsen B, Muenze R. Kinetic investigations on the reaction of technetium (V) gluconate with meso-dimercaptosuccinic acid and meso-dimercaptosuccinic acid dimethylester. *Radiochem. Radioanal. Lett.* **43**, 1980, 311-318.
277. Hwang L L-Y, Ronca N, Solomon NA, Steigman J. Complexes of technetium with polyhydric ligands. *Int. J. Appl. Radiat. Isot.* **36**, 1985, 475-480.
278. Davison A, Orvig C, Trop HS, et al. Preparation of oxobis (dithiolate) complexes of technetium (V) and rhenium(V). *Inorg. Chem.* **19**, 1980, 1988-1992.

279. Bandoli G, Nicolini M, Mazzi U, Spies H, Muenze R. Synthesis and x-ray crystal structure of tetraethylammonium bis [1,2-di (carbomethoxy) ethane-1,2-dithiolato] oxotechnetate (V). *Transition Met. Chem.* 9, 1984, 127-129.
280. Jones AG, DePamphilis BV, Davison A. Preparation and crystal structure of tetraphenylarsonium bis (2-mercaptoethanolato)oxotechnetate. *Inorg. Chem.* 20, 1981, 1617-1618.
281. DePamphilis BV, Jones AG, Davison A. Ligand - exchange reactivity patterns of oxotechnetium (V) complexes. *Inorg. Chem.* 22, 1983, 2292-2297.
282. Davison A, Jones AG, Orvig C, Sohn M. A new class of Oxotechnetium (V) chelate complexes containing a $TcON_2S_2$ core. *Inorg. Chem.* 20, 1981, 1629-1632.
283. Jones AG, Davison A, La Tegola et al. Chemical and in vivo studies of the anion oxo [N,N'-ethylenebis (2-mercaptoacetimido)] technetate (V). *J. Nucl. Med.* 23, 1982, 801-809.
- 283a. Burns HD, Manspeaker H, Miller R et al. Preparation and biodistribution of neutral, lipid-soluble Tc-99m complexes of bis (2-mercaptoethyl)amine ligands. *J.Nucl.Med.* 20, 1979 (abstr.), 654.
- 283b. Lever SZ, Burns HD, Kervitsky TM et al. Design preparation and biodistribution of a technetium-99 triaminodithiol complex to assess regional cerebral blood flow. *J.Nucl.Med.* 26, 1985, 1287-1294
- 283c. Epps LA, Burns HD, Lever SZ et al. Brain imaging agents: synthesis and characterization of (N-piperidinyethyl) hexamethyl diaminodithiolate oxotechnetium(V) complexes. *Appl. Radiat. Isot.* 38, 1987, 661-664.
- 283d. Kung HF, Yu CC, Billings J et al: Synthesis of new bis(aminoethanethiol) (BAT) derivatives: Possible ligands for Tc99m brain imaging agents. *J. Med. Chem.* 28, 1985, 1280-1284.
284. Davison A, Jones AG, Orvig C, et al. A series of oxotechnetium (+ 5) chelate complexes containing a $TcOS_2N_2$ core. *J. Nucl. Med.* 22, 1981, 59.
285. Lockyer TN, Martin RL. Dithiolium salts and Dithio-b-diketone complexes of the transition metals. *Progress in Inorg. Chem.* Lippard SJ ed, Vol. 27, 1980, 222-324.
286. Cotton FA, Wilkinson G. *Advanced Inorganic Chemistry*, 3rd ed. Wiley-Interscience, New York, 1972, 539.
287. Basolo F, Pearson RG. The trans effect in metal complexes in progress. *Inorg. Chem.*, Cotton FA ed., Interscience Publishers, John Wiley & Sons, Inc., NY vol. 4, 1962, 381-453.
288. Muenze R. Formation of citrate complexes of technetium. *Radiochem. Radioanal. Lett.* 30, 1977, 61-64.
289. Strouse J, Layten SW, Strouse CE. Structural studies of transition metal complexes of trionized and tetraionized citrate. Models for the coordination of the citrate ion to transition metal ions in solution and at the active site of aconitase. *J. Am. Chem. Soc.* 99, 1977, 562-572.
290. Strouse J. ^{13}C NMR studies of ferrous citrates in acidic and alkaline solutions. Implications concerning the active site of aconitase. *J. Am. Chem. Soc.* 99, 1977, 572-580.

291. Vanura P, Kuca L. Citrate complexes of iron (III) in solutions of high citrate concentration. Collect. Czech. Chem. Commun. [43](#), 1978, 1460-1475.
292. Martell AE, Smith RM. Critical stability constants. Vol. [3](#), [161-164](#). Plenum Press, NY & London, 1977. Vol. [5](#), 1982, 329-330.
293. Hambright P, McRae J, Valk PE, et al. Chemistry of technetium radiopharmaceuticals. [1](#). Exploration of the tissue distribution and oxidation state consequences of technetium (IV) in Tc-Sn-gluconate and Tc-Sn-EHDP using carrier ^{99}Tc . J. Nucl. Med. [16](#), 1975, 478-482.
294. Steigman J. Chemical state of technetium in vivo (letter No. [2](#)). J. Nucl. Med. [17](#), 1976, 423-424.
295. Clarke MJ, Fackler PH. The chemistry of technetium: toward improved diagnostic agents. Struct. Bonding [50](#), 1982, [57-78](#).
296. Heitzmann MW, Ford LA. Non-aqueous electrophoresis study of complex formation between catechol and technetium (V). J. Chromatog. [267](#), 1983, 213-217.
297. deKieviet W. Technetium radiopharmaceuticals: Chemical characterization and tissue distribution of Tc-Glucoheptonate using Tc-99m and carrier [Tc-99](#). J. Nucl. Med. [22](#), 1981, 703-709.
298. Ritter L. Complexes of tetracycline antibiotics. U.S. [2](#), 736, 725, [2/28/1956](#), Chem. Abst. [50](#), 1956, 10348b.
299. Nakamoto K, McCarthy PJ, Miniatis B. Infrared spectra and normal coordinate analysis of metal-glycolate complexes. Spectrochim. Acta [21](#), 1965, 379-388.
300. Bellamy LJ. The infrared spectra of complex molecules. [Vol.1](#), 3rd edn, Chapman and Hall, England, 1975, 189, 212.
301. Jezowska-Trzebiatowska B, Hanuza J, Baluka M. Force constants and vibration frequencies of the rhenium-oxygen bonds in the infrared region (200-4000 cm^{-1}). Spectrochim. Acta Part A, [27](#), 1971, 1753.
302. Sawyer DT, Brannan JR. Proton-nuclear magnetic resonance studies of several polyalcohols, hydroxy acids and derivatives of D-Gluconic acid. Anal. Chem. [38](#), 1966, 192-198.
303. Owunwanne A, Marinsky JA, Blau M. Determination of the net charge on some Tc-99m radiopharmaceuticals. J. Nucl. Med. [17](#), 1976, 562.
304. Owunwanne A, Marinsky J, Blau M. Ion exchange studies of reduced technetium species and some technetium-99m radiopharmaceuticals. J. Labelled Compd. Radiopharm. [13](#), 1977, [159](#).
305. Moore GE, Kraus KA. Anion exchange studies. IV. Cobalt and nickel in hydrochloric acid solutions. J. Am Chem. Soc. [74](#), 1952, 843-844.
306. Baluka M, Hanuza J, Jezowska Trzebiatowska B. Infrared and electronic spectra of the technetium oxy compounds. Bull Acad. Pol. Sci. Ser. Sci. Chim. [20](#), 1972, 271-278.
307. Cotton FA, Davison A, Day V W et al. Preparation and structural characterization of salts of oxotetrachlorotechnetium (V). Inorg. Chem. [18](#), 1979, 3024-3029.

308. Sawyer DT. Metal-gluconate complexes. Chem. Rev. [64](#), 1964, 633-643.
309. Kuzina AF, Oblova AA, Spitsyn VI. Complexes of technetium IV and V with amines. Russ J. Inorg. Chem. (Eng. transl.) [17](#), 1972, 1377-1379.
310. Simon J, Troutner DE, Volkert WA, Holmes RA. Radiochemical characterization of technetium-cyclam. Radiochem. Radioanal. Lett. [47](#), 1981, [111-123](#).
311. Zuckman SA, Freeman GM, Troutner DE, et al. Preparation and X-ray structure of trans-dioxo ([1,4,8,11](#)-tetraazacyclotetradecane) technetium (V) perchlorate hydrate. Inorg. Chem. [20](#), 1981, 2386-2389.
312. Kastner ME, Lindsay MJ, Clarke MJ. Synthesis and structure of trans-[O₂(en)₂Tc^V]⁺. Inorg. Chem. [21](#), 1982, 2037-2040.
313. Kastner ME, Fackler PH, Clarke MJ, Deutsch E. Synthesis and structure of trans-[O₂(TBP)Tc]⁺ (TBP = [4](#) tert-butylpyridine) and related complexes. Inorg. Chem. [23](#), 1984, 4683-4688.
314. Seifert S, Muenze R, Johannsen B. Cationic technetium complexes with nitrogen-containing ligands: a new group of technetium compounds. Radiochem. Radioanal. Lett. [54](#), 1982, [153-163](#).
315. Siripaisarnpipat S, Schlemper EO. Preparation, spectra and crystal structures of two rhodium (III) complexes with short intramolecular hydrogen bonds. Inorg. Chem. [23](#), 1984, 330-334.
316. Vassian EG, Murmann RK. Aromatization of an aliphatic amine oxime Nickel (II) complex by molecular oxygen. Inorg. Chem. [6](#), 1967, 2043-2046.
317. Troutner DE, Volkert WA, Hoffman TJ, Holmes RA. A neutral lipophilic complex of ^{99m}Tc with a multidentate amine oxime.. Int. J. Appl. Radiat. Isot. [35](#), 1984, 467-470.
318. Fair CK, Troutner DE, Schlemper EO, Murmann RK, Hoppe ML. Oxo [[3,3'-\(1,3-propanediylidimino\) bis \(3-methyl-2-butane oximate\) \(3-\)-N,N',N'',N'''](#)] technetium VI, [Tc O ([C₁₂H₂₄N₄O₂](#))₂]. Acta Crystallogr. Sec. C: Crystal Struct. Commun. [C40](#), 1984, 1544-1546.
319. Jurisson S, Schlemper EO, Troutner DE, Canning LR, Nowotnik DP, Neirinckx RD. Synthesis, characterization and X-ray structural determinations of Technetium (V)-oxo-tetradentate amine oxime complexes. Inorg. Chem. [25](#), 1986, 543-549.
- 319a. Jurisson S, Aston K, Fair C, Key et al. Effect of ring size on properties of technetium amine complexes. X-ray structures of TcO₂ (Pent ([AOI](#))₂) which contains an unusual eight-membered chelate ring and of [TcOEn\(AOI\)₂](#). Inorg. Chem. [26](#), 1987, 3576-3582.
320. Rajec P, Mikulaj V. Preparation of dioxo (8-hydroxyquinolato) technetium (V) chelate by extraction method. Radiochem. Radioanal. Lett. [17](#), 1974, 375-380.
321. Przywarska-Boniecka [H](#), Jezowska-Trzebiatowska B. Complexes of rhenium (V) with 8-hydroxyquinoline. Bull. Acad. Polon. Sci., Ser. Sci. Chim. [13](#), 1965, [67-71](#).
322. Wilcox BE, Haig MJ, Deutsch E. Synthesis and characterization of technetium (V) 8-quinolinolate. X-ray crystal structure of cis-chlorobis (2-methyl-8-quinolato)oxotechnetium (V). Inorg. Chem. [23](#), 1984, 2962-2967.
323. Hwang L L-Y, Steigman J. (Unpublished)

324. Bandoli G, Mazzi U, Clemente DA, Roncari E. Synthesis of six-coordinate technetium (V) complexes with N-phenylsalicylideneimine. X-ray crystal structure of chlorooxobis (N-phenylsalicylideneiminato) technetium (V). *J. Chem. Soc. Dalton Trans.* 1982, 2455-2459.
325. Bandoli G, Mazzi U, Wilcox BE, Jurisson S, Deutsch E. Synthesis and characterization of technetium (V) complexes with tridentate Schiff base ligands. X-ray crystal structure of chloro [N-(2-hydroxyphenyl) salicylidene-iminato] oxotechnetium (V). *Inorg. Chim. Acta* 95, 1984, 217-223.
326. Jurisson S, Lindoy LF, Dancey KP, et al. New Oxotechnetium (V) complexes of N N'-ethylenebis (acetylacetoneimine), N N'-ethylenebis (salicylideneimine) and o-phenylenebis (salicylideneamine). *Inorg. Chem.* 23, 1984, 227-231.
327. Mazzi U, Refosco F, Tisato F, Bandoli G, Nicolini M. Mixed Tri- and Bi-dentate Schiff-base complexes of technetium (V) and Rhenium (V). The crystal structure of [N-(2-oxidophenyl)-salicylideneiminato-NOO'] oxo [8-quinolinolato-NO] Tc (V) . *J Chem. Soc. Dalton Trans.* 1986, 1623-1628.
328. DuPreez JGH, Gerber TIA, Fourie PJ, Van Wyk AJ. The chemistry of rhenium and technetium. Part I. Syntheses and characterization of new dioxo technetium (V) complexes with Schiff base -type ligands. *Inorg. Chim. Acta* 82, 1984, 201-205.
329. Kaden L, Lorenz B, Schmidt K, Sprinz H, Wahren M. Nitrido complexes of technetium (V). *Isotopenpraxis* 17, 1981, 174-175.
330. Rowbottom JF, Wilkinson G. Dithiocarbamate complexes of rhenium (V) and (III). *J. Chem. Soc. Dalton Trans.* 1972, 826-830.
331. Baldas J, Bonnyman J, Pojer PM, Williams GA. Synthesis and structure of bis (diethyldithiocarbamate) nitridotechnetium (V): a technetium-nitrogen triple bond. *J. Chem. Soc. Dalton Trans.* 1981, 1798-1801.
332. Chatt J, Falk CD, Leigh GJ, Paske RJ. Nitrido-complexes of rhenium which contain tertiary phosphines, and attempts to prepare their osmium analogs. *J. Chem. Soc. A*, 1969, 2288-2293.
333. Baldas J, Bonnyman J, Williams GA. Structural studies of technetium complexes. Part 4. The crystal structure of trans, trans-acetonitrile, di-isothiocyanato (nitrido) bis-(triphenylphosphine) technetium (V)-acetonitrile (1/0.5) *J. Chem. Soc. Dalton Trans.* 1984, 833-837.
334. Griffith WP. Transition metal nitrido complexes. *Coordin. Chem. Rev.* 8, 1972, 369-396.
335. Hauck J, Schwochau K. Crystal structure of complex technetium compounds. I. Ditetramethylammonium hexathiocyanatotechnetate (IV). *Inorg. Nucl. Chem. Lett.* 9, 1973, 303-304.
336. Hauck J, Schwochau K, Bucksch R. Crystal structure of complex technetium compounds. II. Tetramethylammonium hexaisothiocyanatotechnetate (V). *Inorg. Nucl. Chem. Lett.* 9, 1973, 927-929.
337. Cotton FA, Robinson WR, Walton RA, et al. Some reactions of the octahalodirhenate(III) ions. Reactions with sodium thiocyanate and the preparation of isothiocyanate complexes of rhenium(III) and rhenium(IV). *Inorg. Chem.* 6, 1967, 929-935.

338. Baldas J, Bonnyman J, Williams GA. Studies of technetium complexes. Use of the Tetrachloronitridotechnetate (VI) anion for the preparation of nitrido complexes of technetium. Crystal structure of bis (8-quinolinethiolato) nitridotechnetium (V). *Inorg. Chem.* 25, 1986, 150-153.
- 338a. Duatti A, Marchi A, Pasqualini R. Formation of the $Tc=N$ multiple bond from the reaction of ammonium pertechnetate with S-methyl dithiocarbamate and its application to the preparation of technetium-99m radiopharmaceuticals. *J. Chem. Soc. Dalton Trans.*, 1990, 3729-3733.
339. Davison A, Jones AG, Mueller L, Tatz R, Trop HS. Synthesis and characterization of oxopentakis (isothiocyanato) metalate (V). Complexes of rhenium and technetium. *Inorg. Chem.* 20, 1981, 1160-1163.
340. Trop HS, Jones AG, Davison A. Technetium cyanide chemistry: synthesis and characterization of technetium (III) and- (V) cyanide complexes. *Inorg. Chem.* 19, 1980, 1993-1997.
- 341a. Glavan KA, Whittle R, Johnson SF, et al. Oxidative addition from a six-coordinate to an eight-coordinate complex, single-crystal structure of $[Tc(diams)_2Cl_2]ClO_4$ and $[Tc(diams)_2Cl_4]PF_6$. *J. Am. Chem. Soc.* 102, 1980, 2103-2104.
- 341b. Bandoli G, Mazzi U, Roncari E, et al. Crystal structures of technetium compounds, *Coordination Chem. Rev.* 44, 1982, 210. Deutsch EA, Elder RC, Packard A, et al. Private Communication.
- 341c. Dilworth JR, Thompson RM, Archer CM, et al. Synthesis of some novel Tc imido complexes in Technetium and Rhenium in Chemistry and Nuclear Medicine 3. Edited by M. Nicolini, G. Bandoli, U. Mazzi, Cortina Int. Raven Press, New York.
342. Spies H, Johannsen B, Muenze R. Synthesis of bis (1,2-dithiolato-oxotechnetate (V) complexes. *Z. Chem.* 20, 1980, 222-223.
343. Steigman J, Hwang L L-Y, Solomon NA. Mixed-ligand complexes of technetium (V). *J. Labelled Compd. Radiopharm.* 16, 1979, 83-85.
344. Linder KE: Aminocarboxylate Complexes of Technetium. -Ph. D. Thesis, M.I. T. June, 1986.
345. Ikeda I, Inoue O, Kurata K. Preparation of various Tc-99m dimercaptosuccinate complexes and their evaluation as Radiotracers. *J. Nucl. Med.* 18, 1977, 1222-1229.
346. Torchinsky YM (Wittenberg Wtranol). Sulfur in Proteins. Pergamon Press, Oxford, New York, etc., 1981, 57-64, 86-88.
347. Schwochau K, Herr W. Preparation, properties and crystal structure of potassium hexafluorotechnetate (IV). *Angew. Chem. Inter. Ed'n (Eng.)* 2, 1963, 97.
348. Colton R, Peacock RD. An outline of technetium chemistry. *Quart. Rev. (London)* 16, 1963, 299-315.
349. Alberto R, Anderegg G. New synthesis of $K_2[TcF_6]$. *Polyhedron* 4, 1985, 1067.
350. Gmelin Handbook of Inorganic Chemistry, System Number 69. Tc Technetium, Supplement Volume 2, Metals, Alloys, Compounds, Chemistry in Solution. Springer-Verlag, Berlin, Heidelberg, New York, 1983, 100.

351. Dalziel J, Gill NS, Nyholm RS, et al. Technetium. Part I. The preparation and properties of potassium hexahalotechnetates. *J. Chem. Soc.*, 1958, 4012-4016.
352. Nelson CM, Boyd GE, Smith WT, Jr. Magnetochemistry of technetium and rhenium. *J. Am. Chem. Soc.* 76, 1954, 348-352.
353. Dorain PR: ARL-73-0139, 1973, 1-47. Magnetic and optical properties of transition metal ions in single crystals. See *Chem. Abstracts* 80, 1974, 65183.
354. Cotton FA, Davison A, Day VW, Gage LD, Trop HS. Preparation and structural characterization of salts of oxochlorotechnetate (V). *Inorg. Chem.* 18, 1979, 3024-3029.
355. Elder M, Fergusson JE, Gainsford GJ, Hickford JH, Penfold BR. Potassium pentachlorohydroxytechnetate (IV). *J. Chem. Soc. (A)* 1967, 1423-1425.
356. Schwochau K. Zur chemie des technetiums. *Angew. Chem.* 76, 1964, 9-19.
357. Boyd GE. Technetium and Promethium. *J. Chem. Ed.* 36, 1959, 3-14.
358. Schwochau K. Comparative crystal structure investigation on potassium and rubidium hexahalotechnetates(IV) and rhenates(IV). *Z. Naturforsch.* 19a, 1964, 1237- 1238.
359. Williams GA, Bonnyman J., Baldas J. Structural studies of technetium complexes X. The crystal structure of tetraphenylarsonium hexakis (isothiocyano) technetate (IV) dichloromethane (1/1)† *Aust. J. Chem.* 40, 1987, 27-33.
360. Jorgensen CK, Schwochau K. Comparative interpretation of absorption spectra of technetium(IV) and rhenium(IV) hexahalides. *Z. Naturforsch.* 20a, 1965, 65-75.
361. Schwochau K, Knappwost A, Burkard E, et al. The magnetic behavior of the the hexahalo complexes of quadrivalent technetium. *Z. Naturforsch.* 19a, 1964, 1128.
362. Basolo F and Pearson RG. Mechanisms of Inorganic Reactions, A study of Metal Complexes in Solution, 2nd edition, John Wiley & Sons. Inc., N.Y. 1967, 145.
363. Gmelin Handbook of Inorganic Chemistry, System Number 69, Tc Technetium, Supplement Volume 2, Metals, Alloys, Compounds, Chemistry in Solution. Springer-Verlag, Berlin, Heidelberg, New York, 1983, 101.
364. Schwochau K. Stability and rate of ligand exchange of the hexachloro- and hexabromo complexes of Tc (IV) and Re (IV). *Z. Naturforsch.* 20a, 1965, 1286.
- 365a. Fujinaga T, Koyama M, Kanchiku Y. Photochemical reaction of technetium (IV) chloro complexes. *Bull. Chem. Soc. Japan* 40, 1967, 2970-2971.
- 365b. Koyama M, Kanchiku Y, Fujinaga T. Photochemical behavior of the hexachlorotechnetate (IV) ion. *Coord. Chem. Rev.* 3, 1968, 285-291.
366. Kawashima M, Koyama M, Fujinaga T. A quation of Hexahalogenato Tc(IV) *J. Inorg. Nucl. Chem.* 38, 1976, 819-822.
367. Janovici E, Kosinski M, Lerch P, Maddock AG. The aquation of hexachlorotechnetate (IV). *J. Radioanal. Chem.* 64, 1981, 321-332.

368. Muenze R, Grossmann B. Hydrolysis of hexachlorotechnetate (IV) and hexabromotechnetate (IV). [Ber] 1975, ZFK-294, 150-153 (a review).
369. Colin M, Ivanovici E, Lerch P, et al. Kinetic study of the aquation of dipotassium technetium hexabromide in perchlorate solutions. J. Radioanal. Nucl. Chem. 92, 1985, 283-292.
370. Rogers LB. Electroreparation of technetium from rhenium and molybdenum. J. Am. Chem. Soc. 71, 1949, 1507-1508.
371. Schwochau K, Herr W. Chemistry of technetium complexes. I. Preparation and properties of cyanotechnetate (IV) Z. Anorg. Allgem. Chem. 318, 1962, 198-211.
372. Colton R, Tomkins IB. Halides and oxide halides of technetium. Aust. J. Chem. 21, 1968, 1981-1985.
373. Steigman J, Solomon NA, Strivstava S. (Unpublished)
374. Steigman J, Solomon NA, Hwang L L-Y. (Unpublished).
375. Boyd GE, Larson QV, Motta EE. Isolation of milligram quantities of long-lived technetium from neutron-irradiated molybdenum. J. Am. Chem. Soc. 82, 1960, 809-815.
376. Gorski B, Koch H. Chemistry of technetium in aqueous solution. I. State of tetravalent technetium in aqueous solution. J. Inorg. Nucl. Chem. 31, 1969, 3565-3571.
377. Noll B, Seifert S, Muenze R. Zur Bildung des Tc(IV)-DTPA(1:1) Komplexes. Zentralinst Kernforsch. Rossendorf. Dresden (Ber.), 1975, 145.
378. Sundrehagen E. Polymer formation and hydrolyzation of tetravalent technetium-99. Int. J. Appl. Radiat. Isot. 30, 1979, 739-743.
379. Owunwanne A, Marinsky J, Blau M. Charge and nature of technetium species produced in the reduction of pertechnetate by stannous ion. J. Nucl. Med. 18, 1977, 1099-1105.
380. Connick RE, McVey WH. The aqueous chemistry of zirconium. J. Am. Chem. Soc. 71, 1949, 3182-3191.
381. Guennec JY, Guillaumont R. Behavior of technetium (IV) in a noncomplexing medium at tracer concentrations. Radiochem. Radioanal. Lett. 1, 1973, 33-38.
382. Meyer RE, Arnold WD and Case FI. Valence effects on solubility and sorption: the solubility of Tc (IV) oxide ORNL-6199; NUREG/CR-4309, March 1986.
383. Schweitzer GK and Jackson M. Radiocolloids. J. Chem. Ed., 1952, 513-522 -a historical review.
384. Haissinsky M. Les Radiocolloides. Hermann et Cie, Paris, 25, 1934.
385. Haissinsky M. Method of preparation of sources of radium E. J. Chim. Phys. 31, 1934, 43-46.
386. Haissinsky M. The solubility of very slightly soluble electrolytes. Acta Physicochem. U.R.S.S. 3, 1935, 517-528.

387. Muenze R. Compounds of technetium (IV) with glycol and glycerol. *Radiochem. Radioanal. Lett.* 31, 1977, 51-56.
- 388a. Hwang L L-Y, Steigman J. Unpublished Results.
- 388b. Alberto R., Andregg G, May K. Synthesis of technetium (IV) alcoholato complexes with methanol, ethyleneglycol and 1,2,4-butanetriol. *Polyhedron* 5, 1986, 2107-2108.
389. Muenze R, Grossmann B. Compounds of technetium (IV) with citric acid. *Radiochem. Radioanal. Lett.* 31, 1977, 95-104.
390. Electrolyte Solutions, Robinson RA and Stokes RH, Academic Press Inc., NY, 1955, 394-406.
391. Muenze R. Polynuclear Technetium-99 (IV)-citrate complex. *Radiochem. Radioanal. Lett.* 48, 1981, 281-287.
392. Wing RM, Callahan KP. The characterization of metal-oxygen bridge systems. *Inorg. Chem.* 8, 1969, 871-874.
393. Muenze R. Formation of technetium III citrate compounds. *Radiochem. Radioanal. Lett.* 30, 1977, 117-122.
394. Muenze R. Electrochemical investigations of the reduction of technetium-99 tetroxide (-) with tin (II) in the presence of citrate. *Radiochem. Radioanal. Lett.* 43, 1980, 215-224.
395. Muenze R, Hoffman I. On the kinetics of reduction of pertechnetate with tin (II) in a citrate medium. *Radiochem. Radioanal. Lett.* 48, 1981, 289-302.
396. Steigman J, Hwang L L-Y, Solomon NA. Magnetic moments of some technetium complexes in D₂O. *J. Labeled Compd. Radiopharm.* 18, 1981, 149.
397. Evans DF. The determination of the paramagnetic susceptibility of substances in solution by nuclear magnetic resonance. *J. Chem. Soc.* 1959, 2003-2005.
398. Jezowska-Trzebiatowska B, Woscichowski W. Theory of bridge bonding and the structure of binuclear coordination compounds in Vol. 6 of *Transition Metal Chemistry*, Carlin RL ed, 1970, Marcel Dekker Inc. NY.
399. Grossmann B, Muenze R. Relationship between complex formation by tetravalent technetium 99 and the chemical structure of aliphatic carboxylic acid ligands. *Int. J. Appl. Radiat. Isot.* 33, 1982, 189-192.
400. Zielkowski J, Baluka M, Jezowska-Trzebiatowska B. Synthesis of technetium (IV) complexes using rhenium (IV) as carrier. *Theory Struct. Complex Compds., Papers Symp.*, Wroclaw, Poland, 419-421, 1962 (Taken from Chemical Abstracts, 63, 1965, 17460).
401. Jezowska-Trzebiatowska B, Wojciechowski W. Para- and diamagnetic Re (IV) Complexes V. The complex of Re (IV) with EDTA. *Bull Acad. Polon. Sci., Ser. Sci. Chem.* 9 (II), 1961, 685-691.
402. Gorski B, Koch H. Technetium complex formation with chelate-forming ligands. II. *J. Inorg. Nucl. Chem.* 32, 1970, 3831-3836.

403. Schubert J, Richter JW. The use of ion exchangers for the determination of physico-chemical properties of substances, particularly radiotracers, in solution. II. The dissociation constants of strontium citrate and strontium tartrate. *J. Phys. Coll. Chem.* 52, 1948, 350-357.
404. Fronaues S. Use of cation exchangers for the quantitative investigation of complex systems. *Acta Chem. Scand.* 5, 1951, 859-871.
405. Noll B, Seifert S, Muenze R. New Tc (IV) compounds with nitrilo- triacetic acid. *Radiochem. Radioanal. Lett.* 43, 1980, 215-218.
406. Seifert S, Noll B, Muenze R. Studies of the complex formation of technetium (IV) with aminopolycarboxylic acids in Aqueous Solution. *Int. J. Appl. Radiat. Isot.* 33, 1982, 1391-1398.
407. Kempf CR, Clark HM, Aikens DA, Bailey RA, Bunce SC, Applebaum G. Electrochemistry of Tc-99 in diethylenetriaminepenta-acetic acid. *J. Nucl. Med.* 21, 1980, 402-403.
408. Blauenstein P, Girgenrath F, Hugli R, et al. Oxidation state of technetium in aminopolycarboxylate complexes. *J. Labelled Compd. Radiopharm* 18, 1981, 194.
409. Burgi HB, Anderegg G, Blauenstein P. Preparation, characterization and crystal, molecular and electronic structure of $(\text{H}_2\text{EDTA})^{99}\text{Tc}^{\text{IV}}(\mu\text{-O})_2^{99}\text{Tc}^{\text{IV}}(\text{H}_2\text{EDTA})_5\text{H}_2\text{O}$. *Inorg. Chem.*, 1981, 3829-3834.
410. Anderegg G., Mueller E, Zollinger K, Burgi HG. Preparation, characterization, crystal and molecular structure of $\text{Na}_2[\text{N}(\text{CH}_2\text{COO})_3]^{99}\text{Tc}(\text{IV})(\mu\text{-O})_2^{99}\text{Tc}(\text{IV})\text{N}(\text{CH}_2\text{COO})_3]_1 \cdot 6\text{H}_2\text{O}$. *Helv. Chim. Acta.* 66, 1983, 1593-1598.
411. Packard AB, Srivastava SC, Richards P, et al. Technetium-99 complexes of oxygen and nitrogen donor ligands. *J. Nucl. Med.* 22, 1981, 70.
412. Johannsen B, Syhre R, Spies H, Munze R. Chemical and biological characterization of different technetium complexes of cysteine and cysteine Derivatives. *J. Nucl. Med.* 19, 1978, 816-824.
413. Yokoyama A, Horiuchi K. Mononuclear and dinuclear complexes of technetium-99m. *Int. J. Appl. Radiat. Isot.* 33, 1982, 929-936.
414. Yokoyama A, Saji H, Tanaka H et al. Preparation of a chemically characterized $^{99\text{m}}\text{Tc}$ -penicillamine complex. *J. Nucl. Med.* 17, 1976, 810-815.
415. Lock, C. Personal communication.
416. Ikeda I, Inoue O and Kurata K: Chemical and biological studies on $^{99\text{m}}\text{Tc}$ -DMS: Effect of Sn(II) on the formation of various Tc-DMS complexes. *Int. J. Appl. Radiat. Isot.* 27, 1976, 681-688.
417. Ikeda I, Inoue O, Kurata K. Preparation of various Tc- $^{99\text{m}}$ dimercaptosuccinate complexes and their evaluation as radiotracers. *J. Nucl. Med.* 18, 1977, 1222-1229.
418. Johannsen B, Spies H, Syhre R. Meso and racemic 2,3 -dimercaptosuccinato technetate(V). *Radiochem. Radioanal. Lett.* 36, 1978, 111-116.
419. Vanlic-Razumenic 'N, Johannsen B, Spies H, et al. Complex of technetium(V) with 2,3 -dimercaptopropane sulfonate, (unithiol): preparation and distribution in the rat. *Int. J. Appl. Radiat. Isot.* 30, 1975, 660-667.

420. Johannsen B, Syhre R, Spies A. Studies in the relation between chemical structure and pharmacokinetic properties of technetium-labeled thiolato complexes. *Nucl. Compact* 11, 1980, 42-44, 48.
421. Vanlic-Razumenic 'N, Petrovic J. Preparation of technetium-99-DMS renal complex in solution and its chemical and biological characterization. *Int. J. Appl. Radiat. Isot.* 33, 1982, 277-284.
422. Yokoyama A, Terauchi Y, Horiuchi K. Technetium-99m-Kethoxal-bis (thiosemicarbazone), an uncharged complex with a tetravalent ^{99m}Tc State, and its excretion into the bile. *J. Nucl. Med.* 17, 1976, 816-819.
423. Thomason PF: U.S. Atomic Energy Commission Report ORNL2 2453, 12/31/57.
424. Hodara I, Silverman C and Balouka I. Electrochemical and Chemical Reduction of pertechnetate *Radiochem. Acta* 18, 1962, 67-71.
425. Steigman J, Meinken G, Richards P. The reduction of pertechnetate-99 by stannous chloride. II. The stoichiometry of the reaction in aqueous solutions of several phosphorus (V) compounds. *Int. J. Appl. Radiat. Isot.* 29, 1978, 653-660.
426. Elmore KL, Hatfield JD, Dunn RL, et al. Dissociation of phosphoric acid solutions at 25'. *J. Phys. Chem.* 69, 1965, 3520-3525.
427. Childs CW. Equilibria in dilute aqueous solutions of orthophosphate. *J. Phys. Chem.* 73, 1969, 2956-2960.
428. Russell CD, Cash AG. Complexes of technetium with pyrophosphate, etidronate and medronate. *J. Nucl. Med.* 20, 1979, 532-537.
429. Russell CD. (Personal communication).
430. Terry AA, Zeitel HE. The determination of technetium by controlled potential coulometric titration in buffered sodium tripolyphosphate medium. *Anal. Chem.* 35, 1963, 614-618.
431. Miller GG, Davis RM, Aikens DA, Clark HM. Chemistry of technetium in tripolyphosphate medium. *Int. J. Appl. Radiat. Isot.* 33, 1982, 897-902.
432. Libson K, Deutsch E, Barnett BL. Structural characterization of a Tc-99 diphosphonate complex. Implications for the Chemistry of technetium- 99m skeletal imaging agents. *J. Am. Chem. Soc.* 102, 1980, 2476-2478.
433. Tanabe S, Zodd JP, Deutsch E, Heineman R. Effect of pH on the formation of Tc (NaBH₄)-MDP radiopharmaceutical analogs. *Int. J. Appl. Radiat. Isot.* 34, 1983, 1577-1584.
434. Pinkerton TC, Heineman WR. The electrochemical reduction of pertechnetate in aqueous hydroxyethylidene diphosphonate media. *J. Electroanal. Chem.* 158, 1983, 323-340.
435. Russell CD, Cash AG. Oxidation state of technetium in bone - scanning agents as determined at carrier concentration by amperometric titration. *Int. J. Appl. Radiat. Isot.* 30, 1979, 485-488.
436. Korteland J, Dekker BG, DeLigny CL. The valence state of technetium-99 in its complexes with bleomycin, 1-hydroxyethylidene-1, 1-diphosphonate and human serum albumin. *Int. J. Appl. Radiat. Isot.* 31, 1980, 315-318.

437. Hambright P, McRae J, Volk PE, Bearden AJ, Shipley BA. Chemistry of technetium radiopharmaceuticals. 1. Exploration of the tissue distribution and oxidation state consequences of technetium (IV) in Tc-Sn-gluconate and Tc-Sn-EHDP using carrier ^{99}Tc . *J. Nucl. Med.* 16, 1975, 478-482.
438. Muenze R. Compounds of technetium (IV) with hydroxyethylidenediphosphonic acid. *J. Labelled Compd. Radiopharm.* 15, 1978, 215.
439. Van den Brand JAGM, Das HA, Dekker BG, DeLigny CL. Gel chromatographic separation and identification of the Technetium (tin)-EHDP complexes using the radiotracers phosphorus-32, technetium-99m, and tin-113. *Int. J. Appl. Radiat. Isot.* 32, 1981, 637-644.
440. Saunders D, Pecsok RL. Calculation of distribution coefficients in inorganic gel chromatography. *Anal. Chem.* 40, 1968, 44-48.
441. Gelotte, B. Studies on gel filtration sorption properties of the bed material Sephadex. *J. Chromatog.* 3, 1960, 330-342.
442. Politi L, Moriggi M, Nicoletti R, Scandurra R. Adsorption chromatography on Bio-Gel P-2. *J. Chromatog.* 267, 1983, 403-408.
443. Pinkerton TC, Desilets CP, Hoch DJ, Mikelsons MV. Bioinorganic activity of technetium radiopharmaceuticals. *J. Chem. Ed.* 62, 1985, 965-973.
444. Pinkerton TC, Heineman WR, Deutsch E. Separation of technetium hydroxyethylidene diphosphonate complexes by anion-exchange high performance liquid chromatography. *Anal. Chem.* 52, 1980, 1106-1110.
445. Wilson GM, Pinkerton TC. Determination of charge and size of technetium diphosphonate complexes by anion-exchange liquid chromatography. *Anal. Chem.* 57, 1985, 246-253.
446. Mikelsons MV, Pinkerton TC. Liquid chromatography of tin-reduced technetium hydroxethylidene diphosphonate complexes for on-line spectral characterization and double isotope labeling. *Anal. Chem.* 58, 1986, 1007-1013.
447. Pinkerton TC, Ferguson DL, Deutsch E et al: *In vivo* distribution of some component fractions of Tc (NaBH₄)-HEDP mixtures separated by anion-exchange high performance liquid chromatography. *Int. J. Appl. Radiat. Isot.* 33, 1982, 907-915.
448. Pinkerton TC, Cheng KT, Shaw SM, Wilson GM. Influence of complex charge and size on the uptake of technetium-99m-diphosphonates in osteogenic tissue. *Nucl. Med. Biol.* 13, 1986, 49-56.
449. Helfferich F. *Ion Exchange*. McGraw-Hill Book Co., NY. 1962, 157.
450. Boyd GE, Soldano BA. Self-diffusion of cations in and through polystyrene cation-exchange polymers. *J. Am. Chem. Soc.* 75, 1953, 6091-6099.
451. Aveston J, Everest DA, Wells RA. Adsorption of gold from cyanide solutions by anionic resins. *J. Chem. Soc.*, 1958, 231-239.
452. Marcus Y, Kertes AS. *Ion exchange and solvent extraction of metal complexes*. Wiley-Interscience, John Wiley and Sons, Inc., New York, 1969, 382-383.

453. Reported in Diamond RM and Whitney DC: Resin selectivity in aqueous solutions, in Ion Exchange Vol. I. J.A. Marinsky Ed, Marcel Dekker, Inc., 1966, 277-351.
454. Cobble JW, Adamson AW. The electron transfer exchange reaction of ferricyanide and ferrocyanide ions. *J. Am. Chem. Soc.* 72, 1950, 2276-2278.
455. Nelson F, Kraus KA. Anion-exchange studies, XXIII. Activity coefficients of some electrolytes in the resin phase. *J. Am. Chem. Soc.* 80, 1958, 4154-4161.
456. Walton, HF, in Chapter 7, of chromatography Part A: Fundamentals and Techniques, E. Heftmann ed., Elsevier Scientific Publishing Co., Amsterdam, Oxford, New York, 1983, A239.
457. Marton A, Inczedy J. Adsorption of differently protonated phosphate ions on anion exchange resins. *Proc. Conf. Appl. Chem. Unit. Oper. Processes*, 3rd, 1977, 97-100. Magy. Kem. Egyesulet: Budapest, Hungary.
458. Antionu NK, Sevryukov NN, Egorov AM: The sorption of carbonate, hydrogen carbonate, chromate and aluminate ions by AV-17 and EDE-10 P Anion Exchange resins in The Bromide Form. *Russ J. Inorg. Chem. (English trans.)* 28, 1983, 94-95.
- 459a. Helffrich F. *Advances in Chromatography*, Vol. I. J.C. Giddings and RA Keller eds, Marcel Dekker, NY, 1965, 3-60.
- 459b. Beukenkamp J, Rieman W (III), Lindenbaum S. Behavior of the condensed phosphates in anion - exchange chromatography. *Anal. Chem.* 26, 1954, 505-512.
- 459c. Lindenbaum S, Peters TV Jr., Rieman W, III. Analysis of mixtures of condensed phosphates by ion-exchange chromatography, *Anal. Chim. Acta* 11, 1954, 530-537.
- 459d. Iguchi A. The separation of polythionates with anion-exchange resins. *Bull. Chem. Soc. Japan* 31, 1958, 597-600.
460. Myers GE, Boyd GE. A thermodynamic calculation of cation - exchange selectivities. *J. Phys. Chem.* 60, 1956, 251-259.
461. Boyd GE, Lindenbaum S, Myers GE. A thermodynamic calculation of selectivity coefficients for strong-base anion exchangers. *J. Phys. Chem.* 65, 1961, 577-586.
462. Lindenbaum S, Boyd GE. Osmotic and activity coefficients for the symmetrical tetraalkylammonium halides in aqueous solution at 25° *J. Phys. Chem.* 68, 1964, 911-917.
463. Robinson RA, Stokes RH. *Electrolyte solutions*. Academic Press, New York, 1955, 479.
464. Gurney RW. *Ionic processes in solution*. McGraw-Hill Book Co., Inc., New York, 1953, 159-171.
465. Frank HS, Wen-Yang Y. Structural aspects of ion-solvent interaction in aqueous solutions: a suggested picture of water structure. *Discuss. Far. Soc.* 24, 1957, 133-140.
466. Gregor HP, Belle J, Marcus RA. Studies on ion-exchange resins. XIII. Selectivity coefficients of quaternary base anion-exchange resins toward univalent anions. *J. Am. Chem. Soc.* 77, 1955, 2713-2719.

467. Fergusson JE, Hickford JH. Complexes of quadrivalent technetium. *J Inorg. Nucl. Chem.* **28**, 1966, 2293-2296.
468. Mazzi U, dePaoli G, diBernardo P, Magon L. Complexes of technetium (IV) and (III) with tertiary phosphines. *J. Inorg. Nucl. Chem.* **38**, 1976, 721-725.
469. Mazzi U, DePaoli G, Traverso O. Technetium complexes with methyl- and ethyldiphenylphosphine. *J. Inorg. Nucl. Chem.* **39**, 1977, 1090-1092.
- 469a. Oblova AA, Kuzina AF, Belyaeva LI et al: Thermal Decomposition of Pyridinium Hexachlorotechnetate: $[\text{PyH}]_2[\text{TcCl}_6]$. *Zh. Neorg. Khim. (Engl. transl.)* **23**, 1978, 1811-1815.
- 469b. Levanda O Yu, Oblova AA, Kuzina AF et al: Structure and properties of the chloride complexes of technetium (IV)- and rhenium (IV)-containing pyridines. *Zh. Neorg. Khim. (Engl. transl)* **30**, 1985, 522-524.
470. Mazzi U, Roncari E, Bandoli G, Magon L. Pentane-2,4-dione complexes of technetium-99. *Transit Met. Chem. (Weinheim, Ger.)* **4**, 1979, 151-155.
471. Miller FS, Zittel HE. Spectrophotometric determination of technetium with 1,5-Diphenylcarbohydrazide. *Anal. Chem.* **35**, 1963, 299-301.
472. Paquette J, Lawrence WE. A spectrochemical study of the technetium (IV)/Technetium (III) couple in bicarbonate solutions. *Can. J. Chem.* **63**, 1985, 2369-2373.
473. Mooney RCL. The crystal structure of element 43. *Acta Cryst.* **1**, 1948, 161-162.
474. Eakins JD, Humphreys DG, Mellish CE. New compounds in which technetium has a low valency. *J. Chem. Soc.* 1963, 6012-6016.
475. Bratton WK, Cotton FA. Characterization of the trinegative octachloroditechnetate Ion. *Inorg. Chem.* **9**, 1970, 789-793.
476. Preetz W, Peters GZ. Preparation and characterization of the tetrabutylammonium salts of octachloroditechnetate (III), $([\text{Tc}_2\text{Cl}_8]^{4-})$, octachloroditechnetate (II,III), $([\text{Tc}_2\text{Cl}_8]^{3-})$, and octabromoditechnetate (III), $([\text{Tc}_2\text{Br}_8]^{3-})$. *Z. Naturforsch. B: Anorg. Chem., Org. Chem* **35B**, 1980, B 797-801.
477. Cotton FA, Daniels L, Davison A, Orvig C. Structural characterization of the octachloroditechnetate (III) Ion in its tetra-n-butylammonium salt. *Inorg. Chem.* **20**, 1981, 3051-3055.
478. Cotton FA, Wilkinson G. *Advanced Inorganic Chemistry*, 5th ed. Wiley-Interscience, New York, 1988, 856.
479. Kryuchkov SV, Kuzina AF, Spitsyn VI. Disproportionation and oxidation by oxygen of octachloroditechnetate (3-) cluster ion in hydrochloric acid solutions. *Zh. Neorg. Khim.* **28**, 1983, 1984-1992.
480. Spitsyn VI, Kuzina AF, Oblova AA, Kryuchkov SV. Chemistry of technetium cluster compounds. *Usp. Khim.* **54**, 1985, 637-670.
481. Jasim F, Magee RJ, Wilson CL. New reagents for the detection of technetium. *Talanta* **2**, 1959, 93-95.

482. Beckmann TJ, Lederer M. Chromatographic par adsorption sur papier. V. Sur Les complexes du rhenium et du technetium Avec La Thiouree. *J. Chromatog.* 5, 1961, 341-350.
483. Morigio L. Thiourea complexes of rhenium and technetium. *Inorg. Chim Acta* 2, 1968, 169-172.
484. Kapunec R, Olah L, Macasek F. Reaction of pertechnetate with thiourea in the nitric acid solutions. *Radiochem. Radioanal. Lett.* 29, 1977, 171-178.
485. Kapunec R, Macasek F, Rajec P, Hudcova D. Ion exchange and solvent extraction of the thiourea complex cation of technetium-99 from mineral - acid solutions. *J Radioanal. Chem.* 51, 1979, 401-405.
486. Abrams MJ, Davison A, Faggiani R, et al. Chemistry and structure of hexakis (thiourea -S) technetium (III) trichloride tetrahydrate, $[Tc(SC(NH_2)_2)_6 Cl_3 \cdot 4H_2O]$. *Inorg. Chem.* 23, 1984, 3284-3288.
- 487a. Muenze R, Grossmann B. Studies on ligand displacement of thiourea in Technetium (III) coordination compounds by chlorine and 1,2 - bis (diphenylphosphine) ethane (dppe). *J. Radioanal. Nucl. Chem.* 86, 1984, 89-95.
- 487b. Russell CD, Speiser AG. Iminodiacetate complexes of technetium: an electrochemical study. *Int. J. Appl. Radiat. Isotopes* 33, 1982, 903-906.
488. Volkert WA, Troutner DE, Holmes RA. Labeling of amine ligands with technetium-99m in aqueous solutions by ligand exchange. *Int. J. Appl. Radiat. Isot.* 33, 1982, 891-896.
489. Wilkins RG, Yelen RE. Kinetics of monomer-dimer interconversion of iron (III) ethylenediaminetetraacetate and related chelates. *Inorg. Chem.* 8, 1969, 1470-1473.
490. Packard AB, Srivastava SC, Richards P, et al. Technetium-99 complexes of oxygen and nitrogen donor ligands. *J. Nucl. Med.* 22, 1981, 70.
491. Bandoli G, Clemente DA, Mazzi U, Roncari E. New form of trans-chlorobis (2,4-pentanedionato) (triphenylphosphine) technetium (III). *Acta Crystallogr.* B34, 1978, 3359-3361.
492. Bandoli G, Clemente DA, Mazzi U; Preparation and molecular structure of trans-chlorobis (pentane-2,4-dionate) (triphenylphosphino) technetium(III). *J. Chem. Soc. Dalton*, 1977, 1837-1844.
493. Fergusson JE, Nyholm RS. New oxidation state of technetium. *Nature* 183, 1959, 1039-1040.
494. Elder RC, Whittle R, Glavan KA, et al. Trans-Dichlorobis (o-phenylenebis (dimethylarsine) technetium (III), perchlorate and chloride salts. *Acta Crystallogr.* B36, 1980, 1662-1665.
495. Fergusson JE, Nyholm RS. Quinquevalent technetium. *Chem. Ind.*, 1960, 347-348.
496. Halpern J. Oxidative - addition reactions of transition metal complexes. *Accts. Chem. Res.* 3, 1970, 386-392.
497. Fergusson JE, Hickford JH. Complexes of quadrivalent technetium. *J. Inorg. Nucl. Chem.* 28, 1966, 2293-2296.

498. Chatt J, Rowe GA. Complex compounds of tertiary phosphines and tertiary arsine with rhenium (V), rhenium (III), and rhenium (II). *J. Chem. Soc.*, 1962, 4019-4032.
499. Mazzi U, DePauli G, Rizzardi G, Magon L. New complexes of technetium (III) and - (IV) with dimethylphenylphosphine. *Inorg. Chim. Acta* 10, 1974, L2.
500. Bandoli G, Clemente DA, Mazzi U. Preparation and crystal and molecular structure of mer-trichlorotris (dimethylphenylphosphine) technetium (III). *J. Chem. Soc. Dalton Trans.* 1976, 125-130.
501. Mazzi U, dePaoli G, Travers O. Technetium complexes with methyl- and ethyldiphenylphosphine *J. Inorg. Nucl. Chem.* 39, 1977, 1090-1092.
502. Fergusson JE, Hevelde PF. Tertiary phosphine complexes of rhenium: a spectroscopic study. *J. Inorg. Nucl. Chem.* 38, 1976, 2231-2237.
503. Deutsch E, Bushong W, Glavan KA, et al. Heart imaging with cationic complexes of technetium. *Science* 214, 1981, 85-86.
504. Mazzochin GA, Seeber R, Mazzi U, Roncari E. Voltammetric behavior of technetium - 99 complexes with n - acceptor ligands in aprotic media. I. Oxidation of trichlorotris (dimethylphenylphosphine) technetium (III). *Inorg. Chim. Acta* 29, 1978, 1-4.
505. Mazzochin GA, Seeber R, Mazzi U, Roncari E. Voltammetric behavior of technetium - 99 complexes with n - acceptor ligands in aprotic medium. II Reduction of trichlorotris dimethylphenylphosphine) technetium IV. *Inorg. Chim. Acta* 29, 1978, 5-9.
506. *Electrochemical Methods: Fundamentals and Applications*, by A.J. Bard and L.R. Faulkner. John Wiley & Sons. N.Y., 1980, 431-433.
507. Libson K, Barnett BL, Deutsch E. Synthesis, characterization and electrochemical properties of tertiary diphosphine complexes of technetium: single-crystal structure of the prototype complex $\text{trans}[\text{Tc}(\text{DPPE})_2\text{Br}_2]\text{BF}_4^-$. *Inorg. Chem.* 22, 1983, 1695-1704.
508. Ichimura A, Heineman WR, Vanderheyden J-L, Deutsch E. Technetium Electrochemistry. 2¹. Electrochemical and spectroelectrochemical studies of the Bis (tertiary phosphine) (D) complexes $\text{trans}[\text{Tc}^{\text{III}}\text{D}_2\text{X}_2]^+$ (X = Cl, Br) and $[\text{Tc}^{\text{I}}\text{D}_3]^+$. *Inorg. Chem.* 23, 1984, 1272-1278.
509. Jurisson SS, Dancy K, McPartlin M, Tasker Pa, Deutsch E. Synthesis, characterization and electrochemical properties of technetium complexes containing both tetradentate Schiff base and monodentate tertiary phosphine ligands: single - crystal structure of $\text{trans}-(\text{N},\text{N}'\text{-ethylenebis}(\text{acetylacetonate iminato}))\text{bis}-(\text{triphenylphosphine})\text{technetium (III) hexafluorophosphate}$. *Inorg. Chem.* 23, 1984, 4743-4745.
510. Ichimura A, Heineman WR, Deutsch E. Technetium Electrochemistry. 3. Spectroelectrochemical studies on the mixed - ligand Technetium (III) complexes $\text{trans}[\text{Tc}(\text{PR}_2\text{R}')_2\text{L}]^+$ where L is a tetradentate Schiff base ligand and $\text{PR}_2\text{R}'$ is a monodentate tertiary phosphine ligand. *Inorg. Chem.* 24, 1985, 2134-2139.
- 510a. Deutsch E, Vanderheyden, J-L, Gerundini P, Libson K, Hirth W, Colombo F, Savi A, Fazio F. Development of nonreducible technetium-99m(III) cations as myocardial perfusion imaging agents: Initial experience in humans. *J. Nucl. Med.* 28, 1987, 1870-1880.

511. Lorenz B, Schmidt K. Reaction of trichlorotris (dimethylphenylphosphine) technetium (III) with dithio ligands. *Zeit. Chem.* 23, 1983, 423.
512. Batsanov AS, Struchkov YT, Lorenz B, Wahren M. Synthesis and crystal and molecular structure of tris (diethyldithiocarbamate) dimethylphenylphosphinetechetium (III), a technetium complex with a coordination number of 7. *Z. Anorg. Allgem. Chem.* 510, 1984, 117-122.
513. Lorenz B, Schmidt K. Tris (diethyldithiocarbamate) dimethylphenyl = phosphinetechetium (IV) - hexafluorophosphate, a new cationic complex of technetium. *Z. Chem.* 24, 1984, 443-444.
514. Biagini CM, Clemente DA, Magon L, Mazzi U. Technetium- phosphine complexes. Diethylphenylphosphonite complexes of technetium (III) and mixed ligand complexes of technetium (I) with carbonyls and diethylphenyl-phosphonite, and crystal and molecular structure of cis- dicarbonyltetrakis (diethylphenylphosphonite) technetium (I) perchlorate. *Inorg. Chim. Acta* 13, 1975, 47-59.
515. Bandoli G, Clemente DA, Mazzi U. Carbonyltrichlorotris (dimethylphenylphosphino) technetium -ethanol (1/1), the first seven-coordinate complex of technetium; position of this molecule in the C_{3v} family. *J. Chem. Soc. Dalton Trans.* 1978, 373-380.
516. Kadin L, Lorenz B, Schmidt K, Sprinz H, Wahren M. Preparation and characterization of dihydrido chlorobis [1,2-bis (diphenylphosphino) ethane] technetium (III). *Z. Chem.* 21, 1981, 232.
517. Freria M, DeMichaelis R, Guisto D. Hydrido and halogenohydrido Complexes of rhenium (III) *J. Inorg. Nucl. Chem.* 29, 1967, 1433-1439.
518. Trop HS, Jones AG, Davison A. Technetium cyanide chemistry: synthesis and characterization of technetium (III) and - (V) cyanide complexes. *Inorg. Chem.* 19, 1980, 1993-1997.
519. Kiernan PM, Griffith WP. Heptacyano complexes of rhenium (III) and molybdenum (II) *Inorg. Nucl. Chem. Lett.* 12, 1976, 377-380.
520. Trop HS, Davison A, Carey GH, et al. Electrochemical studies on halide and pseudo-halide complexes of technetium and rhenium. *J. Inorg. Nucl. Chem.* 41, 1979, 271-.
521. Trop HS, Davison A, Jones AG, Davis MA. The identification and characterization of a six-coordinate hexakisthiocyanototechnetate (IV) and seven-coordinate heptakisthiocyanototechnetate (III). *J. Labelled Compd. Radiopharm.* 16, 1979, 82.
522. Meloche VW, Martin RL, Webb WH. Spectrophotometric determination of rhenium with alpha-furildioxime. *Anal. Chem.* 29, 1957, 527-529.
523. Narayanan A, Umland F. Spectrophotometric investigation of rhenium-dimethylglyoxime complex in solution. *Mikrochim. Acta* 1972, 451-454.
524. Kuzina AF. Photometric determination of technetium with furil dioxime in hydrochloric acid solution. *Zh. Analit. Khim* 17, 1962, 487-488. (Engl. trans.)
525. Linder KE, Gougoutas J, Malley M, Nunn AD, Unger S. A re-assessment of the oxidation state of Tc (DMG)₃ (μ-OH) SnCl₃; evidence for Tc (III). *Proc. 7th Int. Symp. on Radiopharm. Chem., Gronigen, the Netherlands* 1988, 266.

526. Nunn AD, Treher EN, Feld T. Boronic acid adducts of technetium oxime complexes (BATO)s a new class of neutral complexes with myocardial imaging capabilities. *J. Nucl. Med.* 27, 1986, 893.
527. Linder K, Feld T, Juri PN, Nunn AD, Treher, EN. A new technetium agent, SQ 32, 097, which can be used to assess Cerebral Blood Flow. *J. Nucl. Med.* 28, 1987, 592
528. Linder KE, Malley M, Gougoutas J et al. Chemistry of Tc(oxime)₃, (u-OH) SnCl₃ and Tc(Cl)(oxime)₃: neutral intermediates in the synthesis of boron-capped 99-Tc-oxime complexes. *Proc. 7th Int. Symp. on Radiopharm. Chem., Gronigen, the Netherlands, 1988*, 54.
529. Hirth W, Jurisson S, Linder K, Feld T, Nunn AD. Chloro-Hydroxy substitution on technetium dioxime complexes: chemical and biological comparison of TcCl(Dioxime)₂, BR and Tc(OH)(Dioxime)₃. *Proc. 7th Int. symp. Radiopharm. Chem. Gronigen, the Netherlands, 1988*, 48.
530. Cotton FA, Bratton WK. A multiple bond between Tc atoms in an octachloroditechnetate ion. *J. Am. Chem. Soc.* 87, 1965, 921.
531. Cotton FA, Gage LD. The preparation and molecular structure of tetrapivalatodichloroditechnetium (III) and its dirhenium congener: a technetium-technetium quadruple bond. *Nouv. J. Chim.*, 1, 1977, 441-442.
532. Cotton FA, Fanwick PE, Gage LD. Tetra (2-oxypyridinato) chloroditechnetium. A new compound with a Tc-Tc bond of Order 3.5 and a remarkable vibronic absorption spectrum. *J. Am. Chem. Soc.* 102, 1980, 1570-1577.
533. Cotton FA, Schive LW. Structure of tripotassium octachloroditechnetate hydrate. *Inorg. Chem.* 14, 1975, 2032-2035.
534. Bandoli G, Mazzi U, Ichimura A, Libson K, Heineman WR, Deutsch E. An isothiocyanato complex of technetium (II). Spectrochemical and single-crystal X-ray structural studies on trans-[Tc(DPPE)₂(NCS)₂]⁰, where DPPE = 1,2-Bis (diphenylphosphino)ethane. *Inorg. Chem.* 23, 1984, 2898-2901.
535. Jorgensen CK. "Symbiotic" ligands, hard and soft central atoms. *Inorg. Chem.* 3, 1964, 1201-1202.
536. Pearson RG. Antisymbiosis and the Trans effect. *Inorg. Chem.* 12, 1973, 712-713.
537. Orvig C. Investigations of the intermediate - and low- valent chemistry of technetium (Ph D. thesis). *Mass. Inst. of Tech.*, 1981.
538. Linder KE, Davison A, Dewan JC, Costello CE, Maleknia S. Nitrosyl complexes of technetium: synthesis and characterization of [Tc^I(NO)(CNCMe₃)₃]PF₆ and Tc(NO)Br₂(CNCMe₃)₃ and the crystal structure of Tc(NO)Br₂(CNCMe₃)₃. *Inorg. Chem.* 25, 1986, 2085-2089.
539. Abrams MJ, Davison A, Jones AG, Costello C, Pang H. Synthesis and characterization of hexakis (alkyl isocyanide) and hexakis (aryl isocyanide) complexes of technetium (I), *Inorg. Chem.* 22, 1983, 2798-2800.
- 540a. Palm Chr., Fischer EO, Baumgaertner F. Aromatic complexes of metals. LX. Dibenzenetechetium (I) cation in ponderable amounts. *Tetrahedron Letters*, 1962, 253-254.

- 540b .Baumgaertner F, Fischer EO, Zahn V. Chemistry of Nuclear processes. 3. Dibenzenetchnetium(I) cation by element conversion from dibenzenemolybdenum(I). Chem. Ber. 94, 1961, 2198-2203.
- 540c. Baumgaertner F, Fischer EO, Zahn V. A new valence state of technetium. Naturwissenschaften 48, 1961, 478.
541. Fischer EO, Schmidt MW. Dicyclopentadienyltechnetium hydride. Angew. Chem. Int. Ed. Engl. 6, 1967, 93.
542. Fischer EO, Schmidt MW. Aromatic complexes of metals. CX. Five and six ring aromatic n-complexes of technetium-99. Chem. Ber. 102, 1969, 1954-1960.
543. Hileman JC, Huggins DK, Kaesz HD. Derivatives of technetium carbonyl. Synthesis and properties of the carbonyl halides and the pentacarbonyl hydride. Inorg. Chem. 1, 1962, 933-938.
544. Palm Chr., Fischer EO, Baumgaertner F. Cyclopentadienyl technetiumtricarbonyl. Naturwiss. 49, 1962, 279.
545. Fischer EO, Fellmann W. Aromatic complexes of metals. Acylation of cyclopentadienylrhenium tricarbonyl and cyclopentadienyltechnetium tricarbonyl. J. Organometal Chem. 1, 1963, 191-199.
546. Kaden L, Lorenz B, Rummel S, Schmitdt K, Wahren M. Synthesis and characterization of new Tc (I) tricarbonyl complexes. Inorg. Chem. Acta 142, 1988, 1-2.
547. Findeisen M, Kaden L, Lorenz B, Wahren M. ⁹⁹Tc NMR spectroscopy on neutral and cationic Tc (I) carbonyl complexes. Inorg. Chim. Acta 142, 1988, 3-4.
548. Tsutsui M, Ichikawa M, Vohwinkel F, Keinosuke S. Unusual Metalloporphyrins. I. Preparation of chromium mesoporphyrin IX dimethyl ester. J. Am. Chem. Soc. 88, 1966, 854-855.
549. Tsutsui M, Hsung CP, Ostfeld D et al. Unusual metalloporphyrin complexes of rhenium and technetium. J. Am. Chem. Soc. 97, 1975, 3952-3965.
550. Mazzi U, Bismondo A, Kotsev N, Clemente DA. Phosphine carbonyl-technetium (I) and technetium (III) complexes. J. Organomet., Chem. 135, 1977, 177-182.
551. Mazzi U, Roncari E, Seeber R, Mazzocchin GA. Voltammetric behavior of technetium - 99 complexes with n-acceptor ligands in aprotic medium. III Oxidation of technetium (I) complexes with phosphine and carbon monoxide ligands. Inorg. Chim Acta 41, 1980, 95-98.
552. Marchi A, Rossi R, Duatti A et al. Reaction of the technetium (I) carbonyl complexes [Tc (PMe₂Ph)₃ (CO)₂Cl] and [Tc (PPh)₃ (CO)₂Cl] toward pseudo-allyl ligands such as triazenido, formamidinato and acetamidinato. Crystal structures of [Tc (PMe₂Ph)₂ (CO)₂ (p-CH₃C₆H₄N:N:NC₆H₄CH₃)-p] and [Tc (PMe₂Ph)₂ (CO)₂ (C₆H₅N:C (CH₃)₂:NC₆H₅)]]. Inorg. Chem. 24, 1985, 4744-4748.
553. Schwochau K, Herr W. Complex Chemistry of Technetium. II. Preparation and properties of potassium cyanotechnetate (I). Z. Anorg. Allgem. Chem. 319, 1962, 148-158.

- 554a. Clauss D, Lissner A. Über Hexacyanomanganate (I) and hexacyanorhenat (I). Z. Anorg. Allgem. Chem. 297, 1958, 300-310.
- 554b. Abrams MT, Davison A, Brodack JW, Jones AG, Faggiani R, Lock CJ. The Preparation of Technetium (III) compounds in aqueous media. J. Labelled Compd. Radiopharm. 1982, 14, 1596-1597.
- 554c. Abrams MJ, Davison A, Jones AG et al. Synthesis and characterization of hexakis (alkyl isocyanide) and hexakis (aryl isocyanide) complexes of Technetium (I). Inorg. Chem. 1983, 22, 2798-2800.
- 554d. Kennedy CM, Pinkerton TC. Technetium carboxylate complexes III. A new synthetic route to hexakis (isonitrile) technetium(I) salts. Appl. Radiat. Isot. 1988, 39, 1179-1186.
- 554e. Isonitrile Chemistry by I. Ugi, Academic Press, New York City 1971, 218.
555. Kaden L, Lorenz B, Kirmse R, Stach J, Abram U.. Synthesis and characterization of technetium (I) and -II) thionitrosyl complexes. Z. Chem. 25, 1985, 29-30.
556. Hieber W, Herget C. Technetium carbonyl. Angew. Chem. 73, 1961, 579-580.
557. Hileman JC, Huggins DK, Kaesz HD. Technetium Carbonyl. J. Am. Chem. Soc. 83, 1961, 2953-2954.
558. Bailey MF, Dahl LF. The crystal structure of ditechneium decacarbonyl. Inorg. Chem. 4, 1965, 1140-1145.
559. Kaden L, Lorenz B, Schmidt K, Sprinz H, Wahren M. Preparation of the technetium-dinitrogen complex bis [1,2-bis. (diphenylnaphthinoethane) dinitrogentechnetium. Z. Chem. 19, 1979, 305-306.
560. Pelikan P, Boca R. Geometric and electronic factors of dinitrogen activation of transition metal complexes. Coord. Chem. Rev. 55, 1984, 55-112.
561. Husak V, Ulcek J. Long-lived ^{99m}Tc in generator-produced ^{99m}Tc, its determination and significance. Int. J. Appl. Radiat. Isotopes 30, 1979, 165-170.
562. Lamson ML, Kirschner AS, Huhe CE, et al. Generator-produced technetium-99m-labeled pertechnetate (^{99m}TcO₄⁻) carrier-free. J. Nucl. Med. 16, 1975, 639-641.
563. Alvarez J, Coves F, Perez T. Rapid estimation of technetium in molybdenum-99-technetium-99m generators. J. Radioanalytical Chemistry 52, 1979, 471-475.
564. Shukla SK. Reduction of pertechnetate-99m ion by hydrochloric acid. 1. Preparation of chromatographically pure technetium-99m(IV). J. Chromatogr. 151, 1978, 51-57.
565. Williams MJ, Deegan T. Effect of concentration upon the chromatographic behavior of technetium in concentrated hydrochloric acid. J. Chromatogr. 54, 1971, 123-129.
566. Muenze R, Noll B. Reduction of pertechnetate in hydrochloric acid solutions. Isotopenpraxis 11, 1975, 190-194.
567. Cifka J. Lower-oxidation-state ^{99m}Tc in the generator product - its determination and occurrence. Int. J. Appl. Radiat. Isot. 33, 1982, 849-855.

568. Lanteigne D, Hnatowich DJ. The labeling of DTPA-coupled proteins with ^{99m}Tc . *Int. J. Appl. Radiat. Isot.* 35, 1984, 617-.
569. Eckelman W, Richards P. Analytical pitfalls with ^{99m}Tc -labeled compounds. *J. Nucl. Med.* 13, 1972, 202-204..
570. Subramanian G, McAfee JG. Use of sodium borohydride in labeling biologically useful compounds with ^{99m}Tc . *J. Nucl. Med.* 10, 1969, 443.
571. Lebowitz E, Atkins HG, Hauser J et al. ^{99m}Tc -Gelatin: a compound with high renal specificity. *Int. J. Appl. Radiat. Isot.* 22, 1971, 786-789.
572. Subramanian G, McAfee JG. Stannous oxide colloid labelled with ^{99m}Tc or ^{113m}In . In for bone marrow imaging. *J. Nucl. Med.* 11, 1970, 365-366.
573. Pettit WA, DeLand FH, Pepper GH, Blanton L. Characterization of tin-technetium colloid in technetium-labeled albumin preparations. *J. Nucl. Med.* 19, 1978, 387-392.
574. Johnson AE, Gollan F. ^{99m}Tc -dioxide a new radiopharmaceutical for liver scanning. *J. Nucl. Med.* 10, 1969, 346.
575. Johnson AE, Gollan F. ^{99m}Tc -technetium dioxide for liver scanning. *J. Nucl. Med.* 11, 1970, 564-565.
576. Cotton FA, Wilkinson G. Advanced inorganic chemistry. 5th ed., Wiley Interscience, NY, 1988, 817.
577. Solubilities of Inorganic and Metal-Organic Compounds, Fourth Edition by W.F. Linke, American Chemical Society, Washington, D.C., 1958, Vol. II, 573.
578. Schirmen FB Jr., Audrieth LF, Gross ST, et al. The composition and structure of molybdenum blue. *J. Am. Chem. Soc.* 64, 1942, 7543-7545.
- 579a. Charreton B, Meunier R. Reaction of the chlororhenate(IV) with different tungstate polyanions. *C. R. Acad. Sci., Ser. C*, 275, 1972, 945-948.
- 579b. Meikeljohn PT, Pope MT, Prados RA. Synthesis of heteropoly anions in aprotic solvents. Tungstoselenates(V), (VI) and (VII). *J. Am. Chem. Soc.* 96, 1974, 6779-6781.
- 579c. Basova EM, Semenovskaya EN. Formation and stability of a molybdo-rhenate heteropoly complex. *Zh. Neorg. Khim.* 33, 1988, 1174-1179.
- 579d. Semenovskaya EN, Basova EM. Determination of rhenium(V) as a molybdo-rhenate heteropoly complex. *Zh. anal. Khim.* 37, 1982, 2014-2020.
580. Lewis JY, Zodda JP, Deutsch E, et al. Determination of pertechnetate by liquid chromatography with reductive electrochemical detection. *Anal. Chem.* 55, 1983, 708-713.
- 581a. Rulfs CL, Pacer RO, Anderson A. The polarography of aqueous pertechnetate ion. *J. Electroanal. Chem.* 15, 1967, 65-66.
- 581b. Mazzocchin GA, Magno F, Mazzi U, et al. Voltammetric behavior of aqueous technetate(VII) ion. *Inorg. Chim. Acta* 9, 1974, 263-268.

- 581c. Pihlar B. Electrochemical behavior of technetium(VII) in acidic medium. J. Electroanal. Chem. Interfacial Electr. 102, 1979, 351-365.
- 581d. Russell CD. Carrier electrochemistry of pertechnetate. Application to radiopharmaceutical labeling by controlled potential electrolysis at chemically inert electrodes. Int. J. Appl. Radiat. Isot. 28, 1977, 241-249.
582. Love DL, Greendale A.E. Polarographic determination of technetium and ruthenium radionuclides in fission products. Anal. Chem. 32, 1960, 780-786.
583. Grassi J., Rogelet P, Devynck J, Tremillon B. Radiopolarography of technetium(VII) in acidic medium. J. Electroanal. Chem. Interfacial Electrochem. 88, 1978, 97-103.
584. Russell CD. Carrier electrochemistry of pertechnetate. Application to radiopharmaceutical labeling by controlled potential electrolysis at chemically inert electrodes. Int. J. Appl. Radiat. Isotopes 28, 1977, 241-249.
585. Russell CD, Crittenden RC, Cash AG. Determination of net ionic charge on technetium-99m. DTPA and technetium-99m EDTA by a column ion-exchange method. J. Nucl. Med. 21, 1980, 354-360.
586. Wheaton RM, Bauman WC. Properties of strongly basic anion exchange resins. Ind. Eng. Chem. 43, 1961, 1088-1093.
587. Steigman J. Unpublished data.
588. Hwang LL-Y, Ronca N, Solomon AN, et al. Extraction of Tc(V) from radiopharmaceuticals. Int. J. Appl. Radiat. Isot. 35, 1984, 825-830.
589. Rajec P, Mikalaj V. Preparation of dioxo (8-hydroxyquinolate) technetium V chelate by extraction method. Radiochem. Radioanal. Lett. 17, 1974, 375-380.
590. Gerlach JL, Frazier Rg. Spectrophotometric determination of chloride in sweat and serum with diphenylcarbazone. Anal. Chem. 30, 1958, 1142-1146.
591. McRae J, Hambright P, Valk P, et al. Chemistry of ^{99m}Tc tracers,. II. *In vitro* conversion of tagged HEDP-pyrophosphate (bone-seekers) into gluconate renal agent. Effects of Ca and Fe (II) on *in vivo* distribution. J. Nucl. Med. 17, 1976, 208-211.
592. Johannsen B. Reaction of ^{99m}Tc-diphosphonate with N-donor ligands. Int. J. Appl. Radiat. Isot. 33, 1982, 429-432.
593. Volkert WA, Troutner DE, Holmes RA. Labeling of amine ligands with ^{99m}Tc in aqueous solutions by ligand exchange. Int. J. Appl. Radiat. Isot. 33, 1982, 891-896.
594. Marzilli LG, Worley P, Burns HD. A new electrophoretic method for determining ligand: technetium stoichiometry in carrier free ^{99m}Tc-radiopharmaceuticals. J. Nucl Med. 20, 1979, 871-876.
595. Burns D, Sowa DT, Worley P, et al. Electrophoretic determination of charge on carrier-free ^{99m}Tc-labeled complexes. J. Pharm. Sci. 70, 1981, 436-439.

596. Byrne ER, Smith JE. Technetium, complexes of aliphatic thiols. Synthesis and characterization of oxo bis(1,2- and 1,3-dithiolato) technetate(V) anions. *Inorg. Chem.* 18, 1979, 1832-.
597. Hwang L L-Y, Aronson FA, Lopez C, et al. Unpublished data.
598. McAfee JG, Stern HS, Fuega GF et al. ^{99m}Tc labeled serum albumin for scintillation scanning of the placenta. *J. Nucl. Med.* 5, 1964, 936-946.
599. Richards P. Proceedings of the 7th annual meeting of the Japanese Society of Nuclear Medicine, Nov. 17, 18, (1967), Tokyo, Japan. *Jap. Nucl. Med.* 7, 1968, 165-170.
600. Hnatowich DJ. Personal Communication.
601. Kolthoff IM, Sandell EB, Meehan ES, et al. Quantitative Chemical Analysis. 4th Edition, The MacMillan Company, London, 1969, 833-834.
602. Tanford C. Thermodynamic evidence for internal bonding in serum albumin. *Proc. Iowa Acad. Sci* 59, 1952, 206-217.
603. Jirgensons B. Optical rotation and viscosity of nature and denatured proteins. I. Influence of pH, and the stability of various proteins toward several denaturing agents. *Arch. Biochem. Biophys.* 39, 1952, 261-270.
604. Tanford C, Buzzell J, Rand D, et al. The reversible expansion of bovine serum albumin in acid solutions. *J. Am. Chem. Soc.* 77, 1955, 6421-6428.
- 605a. Bro P, Singer SJ, Sturtevant SM. The sedimentation behavior of bovine serum albumin in acid solutions. *J. Am. Chem. Soc.* 77, 1955, 4924-4925.
- 605b. Bro P, Singer SJ, Sturtevant SM. On the aggregation of bovine serum albumin in acid solutions. *J. Am. Chem. Soc.* 80, 1958, 389-393.
- 606a. Aoki K, Foster JF. Electrophoretic demonstration of isomerization of bovine plasma albumin at low pH. *J. Am. Chem. Soc.* 78, 1956, 3538-3539.
- 606b. Aoki K, Foster JF. Electrophoretic behavior of bovine plasma albumin at low pH. *J. Am. Chem. Soc.* 79, 1957, 3385-3393.
- 606c. Aoki K, Foster JF. Electrophoretic and hydrogen ion binding behavior of bovine plasma albumin in the presence of 0.02M thiocyanate ion. *J. Am. Chem. Soc.* 79, 1957, 3393-3396.
- 607a. Steinhardt J, Stocker N.. Effects of high pH and sodium dodecyl sulfate on the hidden tyrosines of human serum albumin. *Biochem.* 12, 1973, 1789-1797.
- 607b. Steinhardt J, Stocker N. Remasking of hidden tyrosines of human serum albumin after exposure to high and low pH. *Biochem.* 12, 1973, 2798-2802.
608. Mirsky AE. Sulfhydryl groups of egg albumin in different denaturing agents. *J. Gen. Physiol.* 24, 1941, 709-723.
609. King TP, Spencer EM. Amino acid sequences of the amino and the carboxyl terminal cyanogen bromide peptides of bovine plasma albumin. *Arch. Biochem. Biophys.* 153, 1972, 627-640.

610. Eckelman WC, Meinken G, Richards P. ^{99m}Tc - human serum albumin. *J. Nucl. Med.* 12, 1971, 707-710.
611. Thomas AW. The theory and application of colloidal behavior, Bogue RH ed., Vol. I, The theory of colloidal behavior, McGraw-Hill Book Co., Inc., New York, 1924, 346-361.
612. Williams MJ, Deegan T. The processes involved in the binding of technetium-99m to human serum albumin. *Int. J. Appl. Radiat. Isot* 22, 1971, 767-774.
613. Sundrehagen E. Formation of ^{99m}Tc -plasmin in presence of gentisic acid using technetium-99m pretreated with concentrated hydrochloric acid and vacuum evaporated. *Int. J. App. Radiat. Isot* 33, 1982, 93-97.
614. Paik CH, Pham LNB, Hong SS et al. The labeling of high affinity sites of antibodies with ^{99m}Tc . *Int. J. Nucl. Med. Biol* 12, 1985, 3-8.
615. Paik CH, Eckelman WC, Reba RC. Transchelation of ^{99m}Tc from low affinity sites to high affinity sites of antibody. *Nucl. Med. Biol.* 13, 1986, 359-362.
616. Rhodes BA et al. Labeling proteins with Tc-99m by ligand exchange. U.S. Patent 4, 305 922, 15 Dec. 1981.
617. Rhodes BA, Burchiel SW. Radiolabeling of antibodies with technetium-99m in radioimmunoimaging and radioimmunotherapy, Rhodes BA and Burchiel SW eds., Elsevier.
618. Childs RL, Hnatowich DJ. Optimum conditions for labeling of DTPA-coupled and antibodies with technetium-99m. *J. Nucl Med.* 26, 1985, 293-299.
619. Kasina S, Vanderheyden JL, Fritzberg AR. Application of diamide dimercaptide N_2S_2 bifunctional chelating agents for ^{99m}Tc labeling of proteins. *Proc. 6th Int. Symp. Radiopharmaceutical Chemistry*, Boston, 29 June-3 July, 1986, 269.
620. Arano Y, Yokoyama A, Magata Y et al. Synthesis and evaluation of a new bifunctional chelating agent for ^{99m}Tc labeling proteins: p-carboxyethylphenyl-glyoxal-di-(N-methylthiosemi carbazon). *Int. J. Nucl. Med. Biol.* 12, 1985, 425.
621. Liang FH, Virzi F, Hnatowich DJ. Serum stability and non-specific binding of technetium-99m labeled diaminodithiol for protein labeling. *Nucl. Med. Biol* 14, 1987, 555-562.
622. Fritzberg AR. Advances in ^{99m}Tc -labeling of antibodies. *Nucl. Med. Stuttgart*, 26, 1987, 7-12.
- 623a. Franz J, Volkert WA, Barefield EK, et al. The production of technetium-99m-labeled conjugated antibodies using a cyclam-based bifunctional chelating agent. *Nuc. Med. Biol.* 14, 1987, 569-572.
- 623b. Abrams, MJ, Juweid M, tenKate CI, Schwartz DA, Hauser MM, Gaul FE, Fuccello AJ, Rubin RH, Strauss HW, Fischman AJ. Technetium -99m-human polyclonal IgG radiolabeled via the hydrazino nicotinamide derivative for imaging focal sites of infection in rats. *J. Nucl. Med.* 31, 1990, 2022-2028.
- 623c. Nicholson T, deVries N, Davison A, Jones AG. Synthesis and characterization of aryl diazenido technetium complexes and their protonation reactions. The X-ray structure of $[\text{TcCl}(\text{PPh}_3)_2(\text{NNC}_6\text{H}_4\text{Br})_2]$ in Technetium and Rhenium in Chemistry and Nuclear Medicine 3. Edited by M. Nicolini, G. Bandoli, U. Mazzi, Raven Press, New York, 95-108.

- 624a. Milbourn PJ, Konishi Y, Meinwald SC, et al. Chain reversals in model peptides. Studies of cysteine-containing cyclic peptides. I. Conformational free energies of cyclization of hexapeptides of sequence AC-Cys-X- Pro-Gly- Y-Cys-NHMe. *J. Am. Chem. Soc.* 109, 1987, 4486-4496.
- 624b. Milbourn PJ, Meinwald YC, Takahashi S, et al. Chain reversals in model peptides etc. II Effects of valyl residues and possible i-to- (i + 3) attractive ionic interactions on cyclization of [Cys⁶][Cys⁶] hexapeptides. *Int. J. Peptide Protein Res.* 31, 1988, 311- 321.
625. References in P. Wardman Molecular mechanisms of oxygen and electron affinic radiosensitizers. *Comments. Int. J. Rad. Biol.* 55, 1989, 175-190.
- 626a. Tucker WD, Green MW, Murrenhoff AP. Die produktion von tragerfreiem Tellur-132, Jod-132, Molybdan-99 und Technetium-99m aus neutronen-bestrahltem Uran durch frackionierte sorption an aluminiumoxyd. *Atompraxis* 5, 1962, 163.
- 626b. Richards P. The technetium-99m generator. *Proc. Symp. Radioactive Pharmaceuticals, ORNL, USAEC Technical Information Center, Oak Ridge, Tennessee (Conf-651111)*, 1965, 323-334.
627. Eckelman, WC, Richards P. Instant 99m-Tc-DTPA. *J. Nucl. Med.* 11, 1978, 761.
628. Runge VM. Intravenous Contrast Media, Chap. 47, in *Magnetic Resonance Imaging. Second Edition, Vol. I*, Edited by CL Partain, RR Price, JA Patton, MV Kulkarni, AE James, Jr. W. B. Saunders Co., Philadelphia, PA 19106.
629. Lauffer RB, Brady TJ. Iron ethylene bis (2-hydroxyphenylglycine) as a hepatobiliary MRI contrast agent. Chap. 50 in *Magnetic Resonance Imaging, Second Edition, Vol. I*, Edited by CL Partain, RR Price, JA Patton, MV Kulkarni, AE James, Jr. W. B. Saunders Co., Philadelphia, PA 19106.
630. Vittadini G, Felder E, Tirone P, Lorusso V. B-19036. A potential new hepatobiliary contrast agent for MR proton imaging. *Invest. Radiol.* 23 (Suppl. 1), 1988, 5246-5248.
631. Holman BL, Jones AG, Lister-James J, Davison A, Abrams MJ, Kirshenbaum JM, Tumei SS, English RJ. A new Tc-99m-labeled myocardial imaging agent, hexakis (t-butylisonitrile)-technetium (I) (Tc-99m TBI) initial experience in the human. *J. Nucl. Med.* 25, 1984, 1350-1355.
632. Johnson LL, Seldin DW, Muschel MJ, Smith KF, Blood D.K, Cannon PJ. Comparison of planar SQ 30,217 and Tl-201 myocardial imaging with coronary anatomy. *Circulation* 76, 1987, IV-217 (abstr.).
633. Seldin DW, Johnson LL, Blood DK, Muschel MJ, Smith KF, Wall RM, Cannon PJ. Myocardial perfusion imaging with technetium-99m SQ 30,217: comparison with thallium-201 and coronary anatomy. *J. Nucl. Med.* 30, 1989, 312-319.
634. Meerdink DJ, Thuber M, Savage S, Leppo JA. Comparative myocardial extraction of two technetium labeled boron oxime derivatives (SQ 30,217, SQ 32,014) and thallium. *J. Nucl. Med.* 29, 1988, 972.
635. Narra RK, Nunn AD, Kuczynski BL, Feld T, Wedeking P, Eckelman WC. A neutral Tc-99m complex for myocardial imaging. *J. Nucl. Med.* 30, 1989, 1830-1837.

636. Narra RK, Feld T, Wedeking P, Matyas J, Nunn AD. SQ 30,217, a technetium 99m labeled myocardial imaging agent which shows no interspecies differences in uptake. *J. Nucl. Med.* 27, 1986, 1051 (abstr.).
637. Eckelman WC. A comparison of the pharmacokinetics of a new Tc-99m labeled myocardial imaging agent, SQ 32,014 with SQ 30,217. *J. Nucl. Med.* 28, 1987, 674 (abstr.).
638. Winchell HS, Horst WD, Braun L, Oldendorf WH, Hattner R, Parker H. N-isopropyl-[¹²³I]p-iodoamphetamine: single pass brain uptake and washout, binding to brain synaptosomes, and localization in dog and monkey brain. *J. Nucl. Med.* 21, 1980, 947.
639. Volkert WA, Hoffman TJ, Seger TM, Troutner DE, Holmes RA. ^{99m}Tc-propylene amine oxime (Tc-99m-PnAO): a potential brain radiopharmaceutical. *Eur. J. Nucl. Med.* 11, 1984, 511-516.
640. Volkert WA, McKenzie EH, Hoffman TJ, Troutner DE, Holmes RA. The behavior of neutral amine oxime chelates labeled with technetium at tracer level. *Int. J. Nucl. Med. Biol.* 11, 1984, 243-246.
641. Holmes RA, Chaplin SB, Royston KG, Hoffman TJ, Volkert WA, Nowotnik DP, Canning LR, Cumming SA, Harrison RC, Higley B, Nechvatal G, Pickett RD, Piper IM, Neirinckx RD. Cerebral uptake and retention of Tc-99m hexamethylpropyleneamine oxime (Tc-99m-HM-PAO). *Nucl. Med. Commun.* 6, 1985, 443-447.
642. Narra RK, Kuczynski BL, Silva D, Nunn AD, Eckelman WC. SQ 32,097: A potential Tc-99m labeled brain imaging agent. *J. Labelled Compd. Radiopharm.* 26, 1988, 60-61.
643. Vallabhajosula S, Zimmerman RE, Picard M, Stritzke P, Mena I, Hellman RS, Tikofsky RS, Stabin MG, Morgan RA, Goldsmith SJ. Technetium-99m ECD: A new brain imaging agent: *in vivo* kinetics and biodistribution studies in normal human subjects. *J. Nucl. Med.* 30, 1989, 599-604.
644. Eckelman WC. The development of single-photon emitting, receptor-binding radiotracers in The Chemistry and Pharmacology of Radiopharmaceuticals. Ed. A.D. Nunn, Marcel Dekker Inc., 1991.
645. Counsell RE, Klausmeier WH. Radiotracer interactions with sex steroid hormone receptor proteins (receptor mapping). In Principles in Radiopharmacology, Vol. 2, Colombetti L, Ed., CRC Press, Boca Raton, FL, 1979, 59.
646. Katzenellenbogen JA, Heiman DF, Carlson KE, Lloyd JE. *In vivo* and *in vitro* steroid receptor assays in the design of estrogen radiopharmaceuticals. In Receptor Binding Radiotracers, Vol. 1. Edited by W. C. Eckelman, CRC Press, Boca Raton, FL 1982, 93.

647. Spencer RP. Radiopharmaceuticals: Structure-activity relationships. Grune & Stratton, New York, 1980.
648. Dannals RF, Burns HD, Marzilli LG, Dannals TE, Kramer AV, Wagner Jr. HN. The use of technetium-99 and technetium-99m in the development and characterization of new radiotracers for diagnostic nuclear medicine. *in* Application of Nuclear and Radiochemistry, Lambrecht RM, Morcos N eds., Pergamon Press, New York, 1982, 127-138.
649. Nowotnik DP. Quantitative structure-distribution relationships (QSDRs) of radiopharmaceuticals. *in* Radiopharmaceuticals: Using Radioactive Compounds in Pharmaceutics and Medicine, Theobald AE ed., Ellis Horwood Ltd., Chichester, 1989, 28-56.
650. Bandoli G, Mazzi U, Roncari E, Deutsch E. Crystal structures of technetium compounds, *Coord. Chem. Rev.* **44**, 1982, 191-227.
651. Srivastava SC, Richards P. Coordination chemistry of technetium as related to nuclear medicine, *J. Indian Chem. Soc.* **69**, 1982, 1262-1269.
652. Davison A. The coordination chemistry of technetium. *in* Technetium in Chemistry and Nuclear Medicine, Deutsch E, Nicolini M, Wagner HN eds., Cortina International, Verona, Italy, 1983, 3-14.
653. Deutsch E, Libson K, Jurisson S, Lindoy LF. Technetium chemistry and technetium radiopharmaceuticals. *in* Progress in Inorganic Chemistry, Lippard SJ ed., J. Wiley & Sons, Inc, New York, 1983, vol. 30, 75-139.
654. Clarke MJ, Podbielski L. Medical diagnostic imaging with complexes of ^{99m}Tc , *Coord. Chem. Rev.* **78**, 1987, 253-331.
655. Melnik M, Van Lier JE. Analyses of structural data of technetium compounds, *Coord. Chem. Rev.* **77**, 1987, 275-324.
656. Dilworth JR. TMC Literature Highlights-24: Recent developments in the coordination chemistry of technetium, *Transition Met. Chem.* **15**, 1990, 411-416.
657. Mazzi U, Nicolini M, Bandoli G, et al. Technetium coordination chemistry: development of new backbones for ^{99m}Tc radiopharmaceuticals. *in* Technetium and Rhenium in Chemistry and Nuclear Medicine 3, Nicolini M, Bandoli G, Mazzi U eds., Cortina International, Verona, Italy, 1990, 39-50.
658. Wei Y, Liu B-L, Kung HF. Quantitative study of the structure-stability relationship of Tc complexes, *Int. J. Appl. Radiat. Isot.* **41**, 1990, 763-772.
659. Nicholson T, de Vries N, Davison A, Jones AG. Synthesis, spectroscopy, and structural characterization of five-coordinate, bis(aryldiazenido)technetium complexes and their protonation reactions. X-ray structure of $[\text{TcCl}(\text{PPh}_3)_2(\text{NNC}_6\text{H}_4\text{Br})_2]$, *Inorg. Chem.* **28**, 1989, 3813-3819.
660. Tulip TH, Calabrese J, Kronauge JF, Davison A, Jones AG. The X-ray molecular structures of hexakis(*t*-butylisonitrile) technetium and rhenium (+1) hexafluorophosphates. *in* Technetium in Chemistry and Nuclear Medicine 2, Nicolini M, Bandoli G, Mazzi U eds., Cortina International, Verona, Italy, 1987, 119-122.
661. Archer CM, Dilworth JR. The synthesis of cations of low oxidation state technetium containing N-donor ligands, *J. Nucl. Med.* **30**, 1989, 939.

662. Breikss AI, Davison A, Jones AG. Low oxidation state chemistry of technetium with nitrogen-donor ligands. *in* Technetium and Rhenium in Chemistry and Nuclear Medicine 3, Nicolini M, Bandoli G, Mazzi U eds., Cortina International, Verona, Italy, 1990, 85-93.
663. De Vries N, Cook J, Davison A, Nicholson T, Jones AG. Synthesis and characterization of a technetium(III) nitrosyl compound: $Tc(NO)(Cl)(SC_{10}H_{13})_3$, *Inorg. Chem.* **29**, 1990, 1062-1064.
664. De Vries N, Davison A, Jones AG. Trigonal bipyridimal compounds of technetium with a tetradentate umbrella ligand, *Inorg. Chim. Acta.* **165**, 1989, 9-10.
665. Costello CE, Brodack JW, Jones AG, et al. The investigation of radiopharmaceutical components by fast atom bombardment mass spectrometry: The identification of Tc-HIDA and the epimers of Tc-CO₂DADS, *J. Nucl. Med.* **24**, 1983, 353-355.
666. Pearlstein RM, Davis WM, Jones AG, Davison A. Preparation and characterization of $TcCl_3(PPh_3)_2(MeCN)$ and its reactions with small pi-accepting ligands, *Inorg. Chem.* **28**, 1989, 3332-3334.
667. Baldas J, Bonnyman J, Mackay MF, Williams GA. Structural studies of technetium complexes. V. The preparation and crystal structure of dichlorobis(diethyldithiocarbamate)thionitrosyltechnetium(III), *Aust. J. Chem.* **37**, 1984, 751-759.
668. Treher EN, Francesconi LC, Gougoutas JZ, Malley MF, Nunn AD. Monocapped tris(dioxime) complexes of technetium(III): Synthesis and structural characterization of $TcX(dioxime)_3B-R$ (X = Cl, Br; dioxime = dimethylglyoxime, cyclohexanedione dioxime, R = CH₃, C₄H₉), *Inorg. Chem.* **28**, 1989, 3411-3416.
669. Linder KE, Malley MF, Gougoutas JZ, Unger SE, Nunn AD. Neutral, seven-coordinate dioxime complexes of technetium(III): synthesis and characterization, *Inorg. Chem.* **29**, 1990, 2428-2434.
670. Martin JL, Yuan J, Lunte CE, Elder RC, Heineman WR, Deutsch E. Technetium-diphosphonate skeletal imaging agents: EXAFS structural studies in aqueous solution, *Inorg. Chem.* **28**, 1989, 2899-2901.
671. Archer CM, Dilworth JR, Jobanputra P, et al. Development of new technetium cores containing technetium-nitrogen multiple bonds. Synthesis and characterization of some diazenido-hydrazido- and imido- complexes of technetium, *Polyhedron* **9**, 1990, 1497-1502.
672. Colmanet SF, Mackay MF. Preparation and structure of bis-μ-(benzene-1,2-dithiolato)bis[(benzene-1,2-dithiolato) technetium(IV)]-chloroform (1:1), *Aust. J. Chem.* **41**, 1988, 269-277.
673. Brenner D, Davison A, Lister-James J, Jones AG. Synthesis and characterization of a series of isomeric oxotechnetium(V) diamido dithiolates, *Inorg. Chem.* **23**, 1984, 3793-3797.
674. Watson AD, Tulip TH, Roe DC. The synthesis, characterization and multinuclear NMR studies of a technetium bisaminebisthiol complex: a new radiopharmaceutical precursor. *in* Technetium in Chemistry and Nuclear Medicine 2, Nicolini M, Bandoli G, Mazzi U eds., Cortina International, Verona, Italy, 1987, 61-64.

675. Jurisson S, Schlemper EO, Troutner DE, Canning LR, Nowotnik DP, Neirinckx RD. The chemistry of technetium(V) complexes containing tetradentate amine oxime ligands: potential brain imaging agents. *in* Technetium in Chemistry and Nuclear Medicine 2, Nicolini M, Bandoli G, Mazzi U eds., Cortina International, Verona, Italy, 1987, 37-41.
676. Morgan GF, Abram U, Evrard G, et al. Structural characterisation of the new brain imaging agent $[^{99m}\text{Tc}][\text{TeO}(\text{L})]$, $\text{H}_3\text{L} = \text{N-4-oxopentan-2-ylidene-N'-pyrrol-2-ylmethylthane-1,2-diamine}$, *J. Chem. Soc. Chem. Commun.*, 1990, 1772-1773.
677. Duatti A, Marchi A, Magon L, Vanderheyden JL, Deutsch E. Tc(V) complexes with Schiff base derivatives of glucosamine. *in* Technetium in Chemistry and Nuclear Medicine 2, Nicolini M, Bandoli G, Mazzi U eds., Cortina International, Verona, Italy, 1987, 131-134.
678. Marchi A, Garuti P, Duatti A, et al. Synthesis of technetium(V)-nitrido complexes with chelating amines: A novel class of monocationic, octahedral complexes containing the $[\text{Tc}\equiv\text{N}]^{2+}$ core. Crystal structures of $[\text{TcN}(\text{en})_2\text{Cl}]^+$ ($\text{en} = \text{ethylenediamine}$) and $[\text{TcN}(\text{tad})\text{Cl}]^+$ ($\text{tad} = 1,5,8,12\text{-tetraazadodecane}$), *Inorg. Chem.* **29**, 1990, 2091-2096.
679. Williams GA. Structural chemistry of nitrido complexes of technetium. *in* Technetium in Chemistry and Nuclear Medicine 2, Nicolini M, Bandoli G, Mazzi U eds., Cortina International, Verona, Italy, 1987, 45-50.
680. deLearie LA, Haltiwanger RC, Pierpont CG. Technetium complexes of 3,5-di-tert-butylcatechol. Direct synthesis of tris(3,5-di-tert-butylcatecholato)technetium(VI) and bis(3,5-di-tert-butylcatecholato)-(di-tert-butylamido phenolato)technetium(VI) from ammonium pertechnetate, *J. Amer. Chem. Soc.* **111**, 1989, 4324-4328.
681. Testa B, Mayer JM. Stereoselective drug metabolism and its significance in drug research. *in* Progress in Drug Research, Jucker E ed., Birkhauser Verlag, Basel, 1988, vol. 32, 249-305.
682. Kasina S, Fritzberg AR, Johnson DL, Eshima D. Tissue distribution properties of the Technetium-99m-diamide-dimercaptide complexes and their potential use as renal radiopharmaceuticals, *J. Med. Chem.* **29**, 1986, 1933-1940.
683. Bormans G, Cleynhens B, Jose D, Hoogmartens M, De Roo M, Verbruggen A. Synthesis and biological characteristics of four stereoisomers of $^{99m}\text{Tc-N,N'bis(mercaptoacetyl)-2,3-diaminopropionate}$, *Int. J. Nucl. Med. Biol.* **17**, 1990, 499-506.
684. Scheffel U, Goldfarb HW, Lever SZ, Gungon RL, Burns HD, Wagner HN. Comparison of technetium-99m aminoalkyl diaminodithiol (DADT) analogs as potential brain blood flow imaging agents, *J. Nucl. Med.* **29**, 1988, 73-82.
685. Neirinckx RD, Canning LR, Piper IM, et al. Technetium-99m d,l-HM-PAO: A new radiopharmaceutical for SPECT imaging of regional cerebral blood perfusion, *J. Nucl. Med.* **28**, 1987, 191-207.
686. Walovitch RC, Hill TC, Garrity ST, et al. Characterization of technetium-99m d,l-L-ECD for brain perfusion imaging, part I: Pharmacology of Tc-99m ECD in nonhuman primates, *J. Nucl. Med.* **30**, 1989, 1892-1901.
687. Volkert WA. Stereoreactivity of ^{99m}Tc -chelates at chemical and physiological levels. *in* Technetium and Rhenium in Chemistry and Nuclear Medicine 3, Nicolini M, Bandoli G, Mazzi U eds., Cortina International, Verona, Italy, 1990, 343-352.

688. Saito Y. Absolute stereochemistry of chelate complexes. *in* Topics in Stereochemistry, Eliel EL, Allinger NL eds., John Wiley & Sons, New York, 1978, vol. 10, 95-174.
689. Solomons TWG. Fundamentals of organic chemistry, 3rd ed. J. Wiley & Sons, Inc, New York.
690. Davison A, Sohn M, Orvig C, Jones AG, LaTegola MR. A tetradentate ligand designed specifically to coordinate technetium, *J. Nucl. Med.* 20, 1979, P641.
691. Fritzberg AR, Klingensmith WC, Whitney WP, Kuni C. Chemical and biological studies of Tc-99m N,N'-bis(mercaptoacetamido)ethylene-diamine: A potential replacement for I-131 iodohippurate, *J. Nucl. Med.* 22, 1981, 258-263.
692. Canning LR, Nowotnik DP, Neirinckx RD, Piper IM. Complexes of technetium-99m with propyleneamine oximes. *Eur. Pat. Appl.* 194,843, 1986.
693. Canning LR, Nowotnik DP. Complexes of technetium-99m with propyleneamine oximes. *Eur. Pat. Appl.* 179,608, 1984.
694. Reichmann K, Biersack HJ, Basso A, et al. A comparative study of brain uptake and early kinetics of Tc-99m-di-HM-PAO and other PnAO derivatives in baboons, *Nuklearmedizin* 25, 1986, 134-137.
695. P.J. Ell, unreported data.
696. Munze R, Abram U, Spies H, Pietzsch HJ. New mixed ligand complexes of technetium (V), (III), (II), and (I). *in* Technetium and Rhenium in Chemistry and Nuclear Medicine 3, Nicolini M, Bandoli G, Mazzi U eds., Cortina International, Verona, Italy, 1990, 177-187.
697. Burns HD, Dannals RF, Marzilli LG, Wagner Jr. HN. Preparation and partial characterisation of aminoethanethiol complexes of carrier free technetium-99m, *J. Nucl. Med.* 20, 1979, 641.
698. Spies H, Scheller D. Stereoisomeric oxotechnetium(V) complexes of 2,3-dimercaptosuccinic acid dimethylester. *in* Technetium in Chemistry and Nuclear Medicine 2, Nicolini M, Bandoli G, Mazzi U eds., Cortina International, Verona, Italy, 1987, 141-143.
699. Fritzberg AR, Kuni CC, Klingensmith WC, Stevens J, Whitney WP. Synthesis and biological evaluation of Tc-99m N,N'-bis(mercaptoacetyl)-2,3-diaminopropionate: a potential replacement for [¹³¹I]-iodohippurate, *J. Nucl. Med.* 23, 1982, 592-598.
700. Rao TN, Wester D, Vanderheyden JL, et al. Structures, stereochemistry, and liquid chromatography properties of technetium and rhenium diamide dimercaptide complexes, *J. Lab. Cmpds. Radiopharm.* 26, 1989, 44-46.
701. Rao TN, Adhikesavalu D, Camerman A, Fritzberg AR. Technetium(V) and Rhenium(V) complexes of 2,3-bis(mercaptoacetamido)propanoate. Chelate ring stereochemistry and influence on chemical and biological properties, *J. Amer. Chem. Soc.* 112, 1990, 5798-5804.
702. Fritzberg AR, Kasina S. Chelating agents for technetium-99m. U.S. Patent 4,670,545, 1987.
703. Schneider RF, Subramanian G, Feld TA, et al. N,N'-(S-bisbenzoylmercaptoacetamido)ethylenediamine and propylenediamine ligands as renal function imaging agents. 1. Alternative synthetic methods, *J. Nucl. Med.* 25, 1984, 223-229.

704. McAfee JG, Subramanian G, Schneider RF, et al. Technetium-99m DADS complexes as renal function and imaging agents: II. Biological comparison with Iodine-131 Hippuran, *J. Nucl. Med.* 26, 1985, 375-386.
705. Fritzberg AR, Kasina S, Eshima D, Johnson DL. Synthesis and biological evaluation of technetium-99m MAG₃ as a Hippuran replacement, *J. Nucl. Med.* 27, 1986, 111-116.
706. Eshima D, Fritzberg AR, Taylor A, Kasina S. Biological studies on a new class of Tc-99m renal tubular function agents. *in* Current Applications in Radiopharmacology; Proc. 4th Int. Symp. Radiopharmacol, Billingham M ed., Pergamon Press, Toronto, 1986, 237-247.
707. Verbruggen A, Bormans G, Cleynhens B, Hoogmartens M, Vandecruys A, De Roo M. Separation of the enantiomers of technetium-99m-MAG₃ and their renal excretion in baboons and a volunteer, *Nuklearmedizin* 25, 1989, 436-439.
708. Bormans G, Cleynhens B, Hoogmartens M, De Roo M, Verbruggen A. Synthesis and biological evaluation of L-alanyl derivatives of ^{99m}Tc-MAG₃. *in* Technetium and rhenium in chemistry and nuclear medicine 3, Nicolini M, Bandoli G, Mazzi U eds., Cortina International, Verona, Italy, 1990, 661-665.
709. Eli PJ, Hocknell JML, Jarritt PH, et al. A Tc-99m-labelled radiotracer for the investigation of cerebral vascular disease, *Nucl. Med. Commun.* 6, 1985, 437-441.
710. Nowotnik DP, Canning LR, Cumming SA, et al. Development of a Tc-99m-labelled radiopharmaceutical for cerebral blood flow imaging, *Nucl. Med. Commun.* 6, 1985, 499-506.
711. Mahmood A, Baidoo KE, Lever SZ. Stereoisomers of neutral oxotechnetium(V) and oxorhenium(V) complexes. *in* Technetium and Rhenium in Chemistry and Nuclear Medicine 3, Nicolini M, Bandoli G, Mazzi U eds., Cortina International, Verona, Italy, 1990, 119-124.
712. Efange SMN, Kung HF, Billings J, Guo Y-Z, Blau M. Technetium-99m bis(aminoethanethiol) complexes with amine side chains - potential brain perfusion imaging agents for SPECT, *J. Nucl. Med.* 28, 1987, 1012-1019.
713. Kung HF, Guo Y-Z, Yu CC, Billings J, Subramanyam V, Calabrese JC. New brain perfusion imaging agents based on ^{99m}Tc-bis(aminoethanethiol) complexes: stereoisomers and biodistribution, *J. Med. Chem.* 32, 1989, 433-437.
714. Mach RH, Kung HF, Jungwiattapanorn P, Guo YZ. Synthesis and biodistribution of a new class of ^{99m}Tc-labeled fatty acid analogs for myocardial imaging, *Int. J. Nucl. Med. Biol.* 18, 1991, 215-226.
715. Yamauchi H, Takahashi J, Seri S, Kawashima H, Koike H, Kato-Azuma M. In vitro and in vivo characterization of a new series of Tc-99m complexes with N₂S₂ ligands. *in* Technetium and Rhenium in Chemistry and Nuclear Medicine 3, Nicolini M, Bandoli G, Mazzi U eds., Cortina International, Verona, Italy, 1990, 475-502.
716. Blondeau P, Berse C, Gravel D. Dimerization of an intermediate during the sodium in liquid ammonia reduction of L-thiazolidine-4-carboxylic acid, *Can. J. Chem.* 45, 1967, 49-52.
717. Edwards DS, Cheesman EH, Watson MW, et al. Synthesis and characterization of technetium and rhenium complexes of N,N'-1,2-diethylenediylbis-L-cysteine. Neurolite and its metabolites. *in* Technetium and Rhenium in Chemistry and Nuclear Medicine 3, Nicolini M, Bandoli G, Mazzi U eds., Cortina International, Verona, Italy, 1990, 433-444.

718. Tulip T. Technetium Chemistry and Radiopharmaceuticals: A Prospectus. Presented at the 194th National Meeting of the American Chemical Society, 1987.
719. Cheesman EH, Blanchette MA, Ganey MV, Maheu LJ, Miller SJ, Watson AD. Technetium-99m ECD: Ester-derivatized diamine-dithiol Tc complexes for imaging brain perfusion, *J. Nucl. Med.* **29**, 1988, 788.
720. Walovitch RC, Makuch J, Knapik J, Watson AD, Williams S. Brain retention of Tc-99m-ECD is related to in vivo metabolism, *J. Nucl. Med.* **29**, 1988, 747.
721. Nosco DL, Verbruggen AM. Technetium-99m complex for examining renal function. U.S. Patent 4,925,650, 1990.
722. Mazzi U, Clemente DA, Bandoli G, Magon L, Orio AA. Technetium-phosphonite complexes. Synthesis of hexacoordinate technetium(II) and technetium(III) complexes of diethyl phenylphosphonite and the crystal structure of dichlorotetrakis(diethyl phenylphosphonite)technetium(II), *Inorg. Chem.* **16**, 1977, 1042-1048.
723. Gerlach DH, Peet WG, Muetterties EL. Stereochemically rigid six-coordinate molecules. II. Preparations and reactions of tetrakis(organophosphorus) metal dihydride complexes, *J. Amer. Chem. Soc.* **94**, 1972, 4545-4549.
724. Vanderheyden JL, Ketring AR, Libson K, et al. Synthesis and characterization of cationic technetium complexes of 1,2-bis(dimethylphosphino)ethane (DMPE). Structure determinations of trans-[TcV(DMPE)₂(OH)(O)](F₃CSO₃)₂, trans-[TcIII(DMPE)₂Cl₂](F₃CSO₃)₂, and [TcI(DMPE)₃]⁺ using x-ray diffraction, EXAFS, and technetium-99 NMR, *Inorg. Chem.* **23**, 1984, 3184-3191.
725. Libson K, Doyle MN, Thomas RW, et al., Structural and kinetic investigations of a Tc(III)/Tc(II) redox couple. X-ray crystal structures of trans-[TcII(DPPE)₂Cl₂] and trans-[TcIII(PDPE)₂Cl₂].HNO₃, where DPPE is 1,2-bis(diphenylphosphino)ethane. *Inorg. Chem.* **27**, 1988, 3614-3619.
726. Kelly JD, Higley B, Archer CM, et al. Technetium-99m complexes of functionalised diphosphines for myocardial imaging. in *Technetium and Rhenium in Chemistry and Nuclear Medicine* 3, Nicolini M, Bandoli G, Mazzi U eds., Cortina International, Verona, Italy, 1990, 405-412.
727. Deutsch EA, Ketring AR, Libson K, Vanderheyden J-L, Hirth WW. The Noah's ark experiment: Species dependent biodistributions of cationic ^{99m}Tc complexes, *Int. J. Nucl. Med. Biol.* **16**, 1989, 191-232.
728. Konno T, Heeg MJ, Deutsch E. Thiolato-technetium complexes. 3. Synthesis and x-ray structural studies on the geometrical isomers cis- and trans-bis(p-chlorobenzenethiolato)bis(1,2-bis(dimethylphosphino)ethane)technetium(II), *Inorg. Chem.* **28**, 1989, 1694-1700.
729. Konno T, Heeg MJ, Deutsch E. Thiolato-Technetium complexes. 1 Synthesis and characterization of bis(tertiary diphosphine)technetium(III) complexes containing methanethiolato ligands. Single-crystal structural analyses of trans-[TcIII(SCH₃)₂(DMPE)₂](CF₃SO₃) and trans-[TcIII(SCH₃)₂(DEPE)₂](PF₆), where DMPE = 1,2-Bis(dimethylphosphino)ethane and DEPE = 1,2-bis(diethylphosphino)ethane, *Inorg. Chem.* **27**, 1988, 4113-4121.

730. Konno T, Kirchhoff JR, Heineman WR, Deutsch E. Thiolato-technetium complexes. 2. Synthesis, characterization, electrochemistry, and spectroelectrochemistry of the technetium(III) complexes $\text{trans-[Tc(SR)}_2\text{(DMPE)}_2\text{]}^+$, where R is an alkyl or benzyl group and DMPE is 1,2-bis(dimethylphosphino)ethane. *Inorg. Chem.* 28, 1989, 1174-1179.
731. Baldas J, Colmanet SF, Mackay MF. Preparation and crystal structures of $[\text{AsPh}_4][\text{Tc}_4\text{N}_4\text{O}_2(\text{ox})_6]$ and $[\text{AsPh}_4]_2[\text{TcO}(\text{ox})_2(\text{Hox})] \cdot 3\text{H}_2\text{O}$: technetium complexes containing quadridentate of unidentate oxalato ligands, *J. Chem. Soc. Dalton Trans.*, 1988, 1725-1731.
732. Wilcox BE, Ho DM, Deutsch E. Synthesis and characterization of mixed-ligand technetium(III) complexes containing halides, phosphines, and either 2,2'-bipyridine, 1,10-phenanthroline, or 2,2':6'2"-terpyridine. X-ray crystal structures of cis(Cl) , $\text{trans(P)-[TcBr(P(CH}_3)_2\text{C}_6\text{H}_5)_2(\text{phen})]$ and $\text{trans(P)-[TcBr(P(CH}_3)_2\text{C}_6\text{H}_5)_2(\text{terpy})]\text{SO}_3\text{CF}_3$, *Inorg. Chem.* 28, 1989, 3917-3923.
733. Wilcox BE, Ho DM, Deutsch E. Synthesis and characterization of technetium(III) complexes containing 2,2'-bipyridine and 1,10-phenanthroline. X-ray crystal structures of cis(Cl) , $\text{trans(P)-[TcCl}_2\text{(P(CH}_3)_2\text{C}_6\text{H}_5)_2\text{(bpy))B(C}_6\text{H}_5)_4]$, cis(Cl) , $\text{trans(P)-[TcCl}_2\text{(P(CH}_3)_2\text{C}_6\text{H}_5)_2(\text{phen})B(C}_6\text{H}_5)_4]$, and cis(Cl) , $\text{trans(P)-[TcCl}_2\text{(P(CH}_3)_2\text{C}_6\text{H}_5)_2(\text{bpy))]\text{SO}_3\text{CF}_3$, *Inorg. Chem.* 28, 1989, 1743-1751.
734. Lu J, Yamano A, Clarke MJ. Synthesis and characterization of technetium(III) complexes with nitrogen heterocycles by oxygen atom transfer from oxotechnetium(V) cores. Crystal structures of $\text{mer-[Cl}_3(\text{pic})_3\text{Tc]}$ and $\text{mer-[Cl}_3(\text{pic})(\text{PMe}_2\text{Ph})_2\text{Tc]}$ ($\text{pic} = 4\text{-picoline}$). Electrochemical parameters for the reduction of TcII , TcIII , and TcIV , *Inorg. Chem.* 29, 1990, 3483-3487.



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